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(71) Applicant *(for all designated States except US):* THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only) :* THAISRIVONGS, Suvit [US/US]; 1327 Edington, Portage, MI 49002 (US).

(74) Agent: WILLIAMS, Sidney, B., Jr.; Patent Law Department, The Upjohn Company, Kalamazoo, MI 49001 (US).

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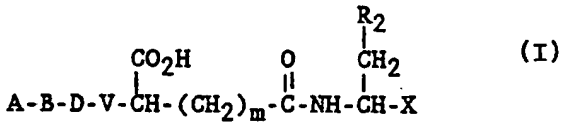
(54) Title: RENIN INHIBITING PEPTIDES THAT CONTAIN AMINO AND HYDROXY DICARBOXYLIC ACIDS



(I)

(57) Abstract

The present invention provides novel renin-inhibiting amino and hydroxy dicarboxylic acid derivatives having transition state inserts of formula (I). Such inhibitors are useful for the diagnosis and control of renin-dependent hypertension and other related diseases.

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RENIN INHIBITING PEPTIDES THAT CONTAIN AMINO AND HYDROXY DICARBOXYLIC ACIDS

DESCRIPTION

BACKGROUND OF THE INVENTION

The present invention provides novel compounds. More particularly, the present invention provides novel renin-inhibiting peptide analogs. Most particularly, the present invention provides renin-inhibitory amino and hydroxy dicarboxylic acid derivatives and having transition state inserts. The renin inhibitors provided herein are useful for the diagnosis and control of renin-dependent hypertension and other related diseases.

Renin is an endopeptidase which specifically cleaves a particular peptide bond of its substrate (angiotensinogen), of which the N-terminal sequence in equine substrate is for example:

Renin
↓
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Leu-Val-Tyr-Ser- IA
1 2 3 4 5 6 7 8 9 10 11 12 13 14

as found by L. T. Skeggs et al, J. Exper. Med. 106, 439 (1957). Human renin substrate has a different sequence as recently discovered by D. A. Tewkesbury et al, Biochem. Biophys. Res. Comm. 99, 1311 (1981). It may be represented as follows:

Renin
↓
-Val-Ile-His-
11 12 13 IB

and having the sequence to the left of the arrow (↓) being as designated in formula IA above.

Renin cleaves angiotensinogen to produce angiotensin I, which is converted to the potent pressor angiotensin II. A number of angiotensin I converting enzyme inhibitors are known to be useful in the treatment of hypertension. Inhibitors of renin are also useful in the treatment of hypertension.

A number of renin-inhibitory peptides have been disclosed. Thus, U.S. Patent 4,424,207; European published applications 45,665; 104,041; and 156,322; and U.S. patent application, Serial No. 825,250, filed 3

February 1986; disclose certain peptides with the dipeptide at the 10,11-position containing an isostere bond. A number of statine derivatives stated to be renin inhibitors have been disclosed, see, e.g., European published applications 77,028; 81,783; 114,993; 156,319; and 156,321; and U.S. patents 4,478,826; 4,470,971; 4,479,941; and 4,485,099. Terminal disulfide cycles have also been disclosed in renin inhibiting peptides; see, e.g., U.S. patents 4,477,440 and 4,477,441. Aromatic and aliphatic amino acid residues at the 10,11-position of the renin substrate are disclosed in U.S. patents 4,478,827 and 4,455,303. C-terminal amide cycles are disclosed in U.S. patent 4,485,099 and European published applications 156,320 and 156,318. Certain tetrapeptides are disclosed in European publications 111,266 and 77,027. Further, European published application No. 118,223 discloses certain renin inhibiting peptide analogs where the 10-11 peptide link is replaced by a one to four atom carbon or carbon-nitrogen link. Additionally, Holladay et al., in "Synthesis of Hydroxyethylene and Ketomethylene Dipeptide Isosteres", Tetrahedron Letters, Vol. 24, No. 41, pp. 4401-4404, 1983 disclose various intermediates in a process to prepare stereo-directed "ketomethylene" and "hydroxyethylene" dipeptide isosteric functional groups disclosed in the above noted U.S. Patent No. 4,424,207. Evans, et al., J. Org. Chem., 50, 4615 (1985) discloses the synthesis of Hydroxyethylene Dipeptide Isosteres. See also published European patent application 163,237 which discloses certain renin inhibiting peptides.

Additionally, published European Applications 45,161 and 53,017 disclose amide derivatives useful as inhibitors of angiotensin converting enzymes.

Certain dipeptide and tripeptides are disclosed in U.S. patents 4,514,332; 4,510,085; and 4,548,926 as well as in European published applications 128,762; 152,255; and 181,110. Pepstatin derived renin inhibitors have been disclosed in U.S. patent 4,481,192. Retroinverso bond modifications at positions 10-11 have been disclosed in U.S. patent 4,560,505 and in European published applications 127,234 and 127,235. Derivatives of isosteric bond replacements at positions 10-11 have been disclosed in European published applications 143,746 and 144,290; and U.S. patent application, Serial No. 904,149, filed 5 September 1986. Isosteric bond modifications at positions 11-12 and 12-13 have been disclosed in European published application 179,352.

Certain peptides containing 2-substituted statine analogues have been disclosed in European published application 157,409. Certain peptides containing 3-aminodeoxystatine have been disclosed in European published application 161,588. Certain peptides containing 1-amino-2-hydroxybutane derivatives at positions 10-11 have been disclosed in European published application 172,346. Certain peptides containing 1-amino-2-hydroxypropane derivatives at positions 10-11 have been disclosed in European published application 172,347. Certain peptides containing N-terminal amide cycles have been disclosed in U.S. patent application, Serial No. 844,716, filed 27 March 1986. Certain peptides containing dihalostatine have been disclosed in PCT application, Serial No. 000,713, filed 7 April 1986. Certain peptides containing C-terminus truncated epoxy or azido or cyano groups or containing a position 10-11 diol and a position 11-12 retro bond have been disclosed in U.S. patent application, Serial No. 945,340, filed 22 December 1986.

European published applications 156,322; 114,993; and 118,223; and PCT patent application, Serial No. 002,227, filed 21 November 1986; U.S. patent application, Serial No. 825,250, filed 3 February 1986; U.S. patent application, Serial No. 904,149, filed 5 September 1986; and U.S. patent application, Serial No. 844,716, filed 27 March 1986; disclose hydroxamic acids or esters at the C-terminus.

E.P. 189,203 discloses new N-dihydroxyalkyl peptide derivatives which are useful as inhibitors of renin for treating hypertension.

E.P. 184,855 discloses new hydroxy substituted-statine peptide derivatives which are useful as inhibitors of renin for treating hypertension.

Derivatives of isosteric bond replacements at positions 10-11 as dihydroxy ethylene isosteres have been disclosed in U.S. patent application, Serial No. 904,149, filed 5 September 1986.

The following references disclose additional substituents at the 10, 11-position: A. Spaltenstein, P. Carpino, F. Miyake and P.B. Hyskins, Tetrahedron Letters, 27:2095 (1986); D.H. Rich and M.S. Bernatowicz, J. Med. Chem., 25:791 (1982); Roger, J. Med. Chem., 28:1062 (1985); D.M. Glick et al., Biochemistry, 21:3746 (1982); D.H. Rich, Biochemistry, 24:3165 (1985); R.L. Johnson, J. Med. Chem., 25:605 (1982); R.L. Johnson and K. Verschovor, J. Med. Chem., 26:1457 (1983); R.L. Johnson, J. Med. Chem., 27:1351 (1984); P.A. Bartlett and W.B. Kezer et al., J. Am. Chem. Soc., 106:4282 (1984); Peptides: Synthesis,

Structure and Function (V.J. Hruby; D.H. Rich, eds.) Proc. 8th American Peptide Sym., Pierce Chemical Company, Rockford, Ill., pp. 511-20; 587-590 (1983).

INFORMATION DISCLOSURE

Certain peptides having cleavable bonds corresponding to the 10,11-position of the renin substrate and containing [malic acid derivatives are disclosed in U.S. Patent 4,629,784 (1986) Stammer; PCT Application WO 85/00809 Stammer]. Different peptides are shown to have different uses such as food additives, analgetics, CNS regulators, renin inhibitors, and antihypertensive agents.

SUMMARY OF THE INVENTION

The present invention provides:

The invention more particularly provides the renin inhibitory peptide of the Formula I

wherein A is

(a) hydrogen,

(b) C_1-C_5 alkyl,

(c) R_3-O-$(CH_2)_q$-C(O)-,

(d) R_3-$(CH_2)_q$-O-C(O),

(e) R_3-O-C(O),

(f) R_3-$(CH_2)_n$-C(O),

(g) $R_1N(R_1)$-$(CH_2)_n$-C(O),

(h) R_3SO_2-$(CH_2)_n$-C(O),

(i) R_3SO_2-$(CH_2)_n$-O-C(O),

(j) R_3S-$(CH_2)_q$-C(O)-,

(k) R_3-$(CH_2)_q$-S-$(CH_2)_n$-C(O)-, or

(l) R_3-$(CH_2)_q$-O-$(CH_{2\_n}$-C(O)-;

wherein B is absent or a divalent moiety of the formula L_1:

wherein D is absent or a divalent moiety of the formula L_2 or L_3:

wherein V is oxygen or -$N(R_1)$-;

wherein X is

-CH(OH)-CH(OH)-CH_2-P,

-E-$C(R_1)(R_4)$-C(O)-F-Z or

-J-$C(K_1)(K_2)$-C(O)-F-Z

wherein P is

(a) -N_3,

(b) -CN,

(c) C_1-C_6 alkyl,

(d) C_1-C_6 cycloalkyl,

(e) aryl, or

(f) Het;

wherein E is a divalent moiety of the formula:

(a) -CH(OH)-,

(b) -CH(NH_2);

(c) -C(O)-,

(d) -CH(OH)-CH(OH)-,

(e) -CH(OH)-CH_2-,

(f) -CH(NH_2)-CH_2-,

(g) -C(O)-CH_2-,

(h) -CH_2-NH-,

(i) -CH_2-O-, or

(j) -P(O)(G)-H-;

wherein F is absent or a divalent moiety of the formula L_3;

wherein G is -OH or NH_2;

wherein H is -O-, -NH-, or -CH_2-;

wherein J is -CH(OH)-, -CH(NH_2)-, or -C(O)-;

where Q is

(a) -CH_2-,

(b) -CH(OH)-,

(c) -O-, or

(d) -S-;

wherein M is

(a) -C(O)-, or

(b) -CH_2-;

wherein K_1 and K2 are H, F, or Cl;

wherein Z is -O-R_5 or -N(R_1)R_5;

wherein R_1 is

(a) hydrogen, or

(b) C_1-C_5 alkyl;

wherein R_2 is

(a) hydrogen

(b) C_1-C_5 alkyl;

(c) C_3-C_7 cyclcoalkyl,

(d) aryl,

(e) het,

(f) -(CH_2)$_p$-OH, or

(g) $-(CH_2)_p-NH_2$;

wherein R_3 is

(a) C_1-C_5 alkyl,

(b) C_3-C_7 cycloalkyl,

(c) aryl, or

(d) het;

wherein R_4 is

(a) hydrogen,

(b) C_1-C_5 alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-het,

(e) C_3-C_7 cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_5 is

(a) hydrogen,

(b) aryl,

(c) het,

(d) C_1-C_{10} alkyl,

(e) $-(CH_2)_p-(C_3$-C_7 cycloalkyl), or

(f) $-(CH_2)_n-R_6$;

wherein R_6 is

(a) aryl,

(b) het,

(c) hydroxy,

(d) amino,

(e) polyhydroxylated alkyl,

(f) -COOH,

(g) guanidyl, or

(h) $-SO_3H$;

wherein m is 1 or 2;

wherein n is 1 to 5, inclusive;

wherein p is 0 to 5, inclusive;

wherein q is 1 to 5, inclusive;

wherein Aryl is phenyl or naphthyl substituted by zero to 3 of the following:

(a) C_1-C_3 alkyl,

(b) hydroxy,

(c) hydroxy(C_1-C_3 alkyl),

(d) halogen,

(e) amino,

(f) amino(C_1-C_3 alkyl),

(g) -CHO,

(h) -CO_2H,

(i) -CO_2-(C_1-C_3 alkyl),

(j) -$CONH_2$,

(k) -CONH-(C_1-C_3 alkyl),

(l) nitro,

(m) mercapto,

(n) mercapto(C_1-C_3 alkyl),

(o) -SO_3H,

(p) -SO_2NH_2,

(q) -CN-;

wherein HET is a 5 ot 6-membered saturated or unsaturated ring containing from one to three heteroatoms (nitrogen, oxygen, sulfur); and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; and, if chemically feasible, the nitrogen and sulfur atoms may be in the oxidized forms;

or a carboxy-, amino- or other reactive group-protected form thereof;

or a pharmaceutically acceptable acid or base addition salts thereof.

Preferred compounds of this invention have the Formula II wherein the stereochemistry at the 2, 4 and 5 carbon is of the S configuration and wherein A is selected from the group consisting of R_3-O-$(CH_2)_q$-C(O)-, R_3-$(CH_2)_n$-C(O)- and R_3S-$(CH_2)_q$-C(O)-; V is oxygen or -N(R1)-; R_2 is C_1-C_5 alkyl or C_3-C_7 cycloalkyl; R_1 is hydrogen or C_1-C_5 alkyl; R_4 is hydrogen or C_1-C_5 alkyl; F is absent or a divalent moiety of the formula L_3; and Z is $N(R_1)R_5$ wherein R_5 is (C_1-C_{10}) alkyl or -(CH_2)-Het.

By "renin inhibitory peptide" is meant a compound capable of inhibiting the renin enzyme in mammalian metabolism and linked by peptidic or pseudo-peptidic bonds.

By "a non-cleavable transition state insert" is meant a transition state insert which is not cleavable by a hydrolytic enzyme in mammalian metabolism. A variety of such transition state inserts, corresponding

to the 10,11-position of the renin substrate, are known in the art, including those disclosed in the following references:

U.S. Patent 4,424,207 (Szelke); European Patent 104041A (Szelke); European Patent Application 144,290A (Ciba Geigy AG); European Patent 0,156,322 (Merck); European Patent 161-588A (Merck); European Patent 0,172,347 (Abbott); European Patent 172-346-A (Abbott); European Patent 156-318 (Merck); European Patent 157-409 (Merck); European Patent 152-255 (Sankyo); and U.S. Patent 4,548,926 (Sankyo); and

U.S. patent application, Serial No. 904,149, filed 5 September 1986; U.S. patent application, Serial No. 844,716, filed 27 March 1986; PCT application, Serial No. 000,713, filed 7 April 1986; U.S. patent application, Serial No. 945,340, filed 22 December 1986; and U.S. patent application, Serial No. 825,250, filed 3 February 1986; and

A. Spaltenstein, P. Carpino, F. Miyake and P.B. Hyskins, Tetrahedron Letters, 27:2095 (1986); D.H. Rich and M.S. Bernatowicz, J. Med. Chem., 25:791 (1982); Roger, J. Med. Chem., 28:1062 (1985); D.M. Glick et al., Biochemistry, 21:3746 (1982); D.H. Rich, Biochemistry, 24:3165 (1985); R.L. Johnson, J. Med. Chem., 25:605 (1982); R.L. Johnson and K. Verschovor, J. Med. Chem., 26:1457 (1983); R.L. Johnson, J. Med. Chem., 27:1351 (1984); P.A. Bartlett et al., J. Am. Chem. Soc., 106:4282 (1984); and Peptides: Synthesis, Structure and Function (V.J. Hruby; D.H. Rich, eds.) Proc. 8th American Peptide Sym., Pierce Chemical Company, Rockford, Ill., pp. 511-20; 587-590 (1983).

As is apparent to those of ordinary skill in the art, the renin inhibitory peptides of the present invention can occur in several isomeric forms, depending on the configuration around the asymmetric carbon atoms. All such isomeric forms are included within the scope of the present invention. Preferably, the stereochemistry of the other amino acids corresponds to that of the naturally-occurring amino acids.

Renin inhibitory peptides commonly have protecting groups at the N-terminus and the C-terminus. These protecting groups are known in the polypeptide art. Examples of these protecting groups are given below. Any of these protecting groups are suitable for the renin inhibitory peptides of the present invention.

Furthermore, the derivative of Formula I of the present invention may occur at the N-terminus of the renin inhibitory peptide and, as such, will, when coupled with a suitable protecting group, assume the ending position.

These compounds are shown in relation to the human renin substrate as follows:

6	7	8	9	10	11	12	13
-His	Pro	Phe	His	Leu	Val	Ile	His-

The present invention provides peptide inhibitors of renin which are derivatives and contain at least one amino acid and have transition state inserts.

Examples of pharmaceutically acceptable acid addition salts include: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix (C_i-C_j) indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus (C_1-C_4)alkyl refers to alkyl of one to 4 carbon atoms, inclusive, or methyl, ethyl, propyl, butyl, and isomeric forms thereof. C_4-C_7 cyclic amino indicates a monocyclic group containing one nitrogen and 4 to 7 carbon atoms.

Examples of (C_3-C_{10})cycloalkyl which include alkyl-substituted cycloalkyl containing a total of up to 10 total carbon atoms, are cyclopropyl, 2-methylcyclopropyl, 2,2-dimethylcyclopropyl, 2,3-diethylcyclopropyl, 2-butylcyclopropyl, cyclobutyl, 2-methylcyclobutyl, 3-propylcyclobutyl, cyclopentyl, 2,2-dimethylcyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and isomeric forms thereof.

Examples of aryl include phenyl, naphthyl, (o-, m-, p-)tolyl, (o-, m-, p-)ethylphenyl, 2-ethyl-tolyl, 4-ethyl-o-tolyl, 5-ethyl-m-tolyl, (o-, m-, or p-)propylphenyl, 2-propyl-(o-, m-, or p-)tolyl, 4-isopropyl-2,6-xylyl, 3-propyl-4-ethylphenyl, (2,3,4- 2,3,6-, or 2,4,5-)-trimethylphenyl, (o-, m-, or p-)fluorophenyl, (o-, m-, or p-trifluoromethyl)phenyl, 4-fluoro-2,5-xylyl, (2,4-, 2,5-, 2,6-, 3,4-, or 3,5-)di-

fluorophenyl, (o-, m-, or p-)chlorophenyl, 2-chloro-p-tolyl, (3-, 4-, 5- or 6-)chloro-o-tolyl, 4-chloro-2-propylphenyl, 2-isopropyl-4-chlorophenyl, 4-chloro-3-fluorophenyl, (3- or 4-)chloro-2-fluorophenyl, (o-, m-, or p-)trifluoro-methylphenyl, (o-, m-, or p-)ethoxyphenyl, (4- or 5-)chloro-2-methoxy-phenyl, and 2,4-dichloro(5- or 6-)methylphenyl, and the like.

Examples of -Het include: 2-, 3-, or 4-pyridyl, imidazolyl, indolyl, N^{in}-formyl-indolyl, N^{in}-C_1-C_5alkyl-C(O)-indolyl, [1,2,4]-triazolyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-thienyl, piperidinyl, pyrryl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, pyrazinyl, piperazinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, and benzothienyl. Each of these moieties may be substituted as noted above.

As would be generally recognized by those skilled in the art of organic chemistry, a heterocycle as defined herein for -Het would not be bonded through oxygen or sulfur or through nitrogen which is within a ring and part of a double bond.

Halo is halogen (fluoro, chloro, bromo, or iodo) or trifluoromethyl.

Examples of pharmaceutically acceptable cations include: pharmacologically acceptable metal cations, ammonium, amine cations, or quaternary ammonium cations. Especially preferred metal cations are those derived from the alkali metals, e.g., lithium, sodium, and potassium, and from the alkaline earth metals, e.g., magnesium and calcium, although cationic forms of other metals, e.g., aluminum, zinc, and iron are also within the scope of this invention. Pharmacologically acceptable amine cations are those derived from primary, secondary, or tertiary amines.

The novel peptides herein contain both natural and synthetic amino acid residues. These residues are depicted using standard amino acid abbreviations (see, e.g., Eur. J. Biochem., 138, 9 (1984)) unless otherwise indicated.

In addition to the treatment of warm-blooded animals such as mice, rats, horses, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

The renin inhibitors of this invention are useful for treating any medical condition for which it is beneficial to reduce the levels of active circulating renin. Examples of such conditions include renin-associated hypertension and hyperaldosteronism, hypertension, hypertension under treatment with another antihypertensive and/or a diuretic agent, congestive heart failure, angina, and post-myocardial infarction. The renin-angiotension system may play a role in maintenance of intracellular homeostasis: see Clinical and Experimental Hypertension, 86, 1739-1742 (1984) at page 1740 under Discussion. Procedures for determining the renin-inhibiting activity of peptides are described in co-pending application Serial No. 825,250 filed February 3, 1986 which is hereby expressly incorporated by reference.

Further, the renin inhibitors of this invention may be useful in the treatment of cerebrovascular disorders and disorders of intracellular homeotasis. The possible role of the renin-angiotensin system in the maintenance of intracellular homeostasis is disclosed in Clinical and Experimental Hypertension, 86:1739-1742 (1984). Additionally, the renin inhibitors of this invention potentiate the antithrombotic activity of a thromboxane antagonist (U.S. patent 4,558,037). The antihypertensive effect of the renin inhibitors of this invention are potentiated by combination with a thromboxane synthetase inhibitor.

The compounds of the present invention are preferably orally administered to humans to effect renin inhibition for the purpose of favorably affecting blood pressure. For this purpose, the compounds are administered from 0.1 mg to 100 mg per kg per dose, administered from 1 to 4 times daily. The compounds of the present invention are preferably orally administered in the form of pharmacologically acceptable acid addition salts. Preferred pharmacologically acceptable salts for oral administration include the citrate and aspartate salts, although any pharmacologically acceptable salt is useful in this invention, including those listed above. These salts may be in hydrated or solvated form.

Other routes of administration include parenteral, by inhalation spray, or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example as a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Equivalent dosages for such other routes of administration are thus employed. The exact dose depends on the age, weight, and condition of the patient and on the frequency and route of administration. Such variations are within the skill of the practitioner or can readily be determined.

The compounds of the present invention may be in the form of pharmaceutically acceptable salts both those which can be produced from the free bases by methods well known in the art and those with which acids have pharmacologically acceptable conjugate bases.

Conventional forms and means for administering renin-inhibiting compounds may be employed and are described, e.g., in U.S. Patent No. 4,424,207 which is incorporated by reference herein. Likewise, the amounts disclosed in the U.S. Patent No. 4,424,207 are examples applicable to the compounds of the present invention.

The renin-inhibiting compounds of this invention may be administered in combination with other agents used in antihypertensive therapy such as diuretics, α and/or β-adrenergic blocking agents, CNS-acting agents, adrenergic neuron blocking agents, vasodilators, angiotensin I converting enzyme inhibitors, and the like as described, for example, in published European patent application 156 318.

For example, the compounds of this invention can be given in combination with such compounds or salts or other derivative forms thereof as:

Diuretics: acetazolamide; amiloride; bendroflumethiazide; benzthiazide; bumetanide; chlorothiazide; chlorthalidone; cyclothiazide;

ethacrynic acid; furosemide; hydrochlorothiazide; hydroflumethiazide; indacrinone (racemic mixture, or as either the (+) or (-) enantiomer alone, or a manipulated ratio, e.g., 9:1 of said enantiomers, respectively); metolazone; methyclothiazide; muzolimine; polythiazide; quinethazone; sodium ethacrynate; sodium nitroprusside; spironolactone; ticrynaten; trimaterene; trichlormethiazide;

α-Adrenergic Blocking Agents: dibenamine; phentolamine; phenoxybenzamine; prazosin; tolazoline;

β-Adrenergic Blocking Agents: atenolol; metoprolol; nadolol; propranolol; timolol;

((±)-2-[3-(tert-butylamino)-2-hydroxypropoxy]-2-furananilide) (ancarolol);

(2-acetyl-7-(2-hydroxy-3-isopropylaminopropoxy)benzofuran HCl)(befunolol);

((±)-1-(isopropylamino)-3-(p-(2-cyclopropylmethoxyethyl)-phenoxy)-2-propranol HCl) (betaxolol);

(1-[(3,4-dimethoxyphenethyl)amino]-3-(m-tolyloxy)-2-propanol HCl)(bevantolol);

(((±)-1-(4-((2-isopropoxyethoxy)methyl)phenoxy)-3-isopropylamino-2-propanol)fumarate) (bisoprolol);

(4-(2-hydroxy-3-[4-(phenoxymethyl)-piperidino]-propoxy)-indole); (carbazolyl-4-oxy-5,2-(2-methoxyphenoxy)-ethylamino-2-propanol);

(1-((1,1-dimethylethyl)amino)-3-((2-methyl 'H-indol-4-yl)oxy)-2-propanol benzoate) (bopindolol);

(1-(2-exobicyclo[2.2.1]-hept-2-ylphenoxy)-3-[(1-methylethyl)-amino]-2-propanol HCl) (bornaprolol);

(o-[2-hydroxy-3-[(2-indol-3-yl-1,1-dimethylethyl)-amino]propoxy]-benzonitrile HCl) (bucindolol);

(α-[(tert.butylamino)methyl]-7-ethyl-2-benzofuranmethanol) (bufuralol);

(3-[3-acetyl-4-[3-(tert.butylamino)-2-hydroxypropyl]-phenyl]-1,1-diethylurea HCl) (celiprolol);

((±)-2-[2-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]phenoxy]-N-methylacetamide HCl) (cetamolol);

(2-benzimidazolyl-phenyl(2-isopropylaminopropanol));

((±)-3'-acetyl-4'-(2-hydroxy-3-isopropylaminopropoxy)-acetanilide HCl) (diacetolol);

(methyl-4-[2-hydroxy-3-[(1-methylethyl)aminopropoxyl]]-benzene-

propanoate HCl) (esmolol);

(erythro-DL-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol); (1-(tert.butylamino)-3-[0-(2-propynyloxy)phenoxy]-2-propanol (pargolol);

(1-(tert.butylamino)-3-[o-(6-hydrazino-3-pyridazinyl)phenoxy]-2-propanol diHCl) (prizidilol);

((-)-2-hydroxy-5-[(R)-1-hydroxy-2-[(R)-(1-methyl-3-phenylpropyl)-amino]ethyl]benzamide);

(4-hydroxy-9-[2-hydroxy-3-(isopropylamino)-propoxy]-7-methyl-5H-furo[3,2-g][1]-benzopyran-5-one) (iprocrolol);

((-)-5-(tert.butylamino)-2-hydroxypropoxy]-3,4-dihydro-1-(2H)-naphthalenone HCl) (levobunolol);

(4-(2-hydroxy-3-isopropylamino-propoxy)-1,2-benzisothiazole HCl); (4-[3-(tert.butylamino)-2-hydroxypropoxy]-N-methylisocarbostyril HCl);

((±)-N-2-[4-(2-hydroxy-3-isopropylaminopropoxy)phenyl]ethyl-N'-isopropylurea) (pafenolol);

(3-[[(2-trifluoroacetamido)ethyl]amino]-1-phenoxypropan-2-ol); (N-(3-(o-chlorophenoxy)-2-hydroxypropyl)-N'-(4'-chloro-2,3-dihydro-3-oxo-5-pyridazinyl)ethylenediamine);

((±)-N-[3-acetyl-4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy-phenyl]-butanamide) (acebutolol);

((±)-4'-[3-(tert-butylamino)-2-hydroxypropoxy]spiro[cyclohexane-1,2'-indan]-1'-one) (spirendolol);

(7-[3-[[2-hydroxy-3-[(2-methylindol-4-yl)oxylpropyl]amino]butyl]thio-phylline) (teoprolol);

((±)-1-tert.butylamino-3-(thiochroman-8-yloxy)-2-propanol) (tertato-lol);

((±)-1-tert.butylamino-3-(2,3-xylyloxy)-2-propanol HCl) (xibenolol);

(8-[3-(tert.butylamino)-2-hydroxypropoxy]-5-methylcoumarin) (bucumo-lol);

(2-(3-(tert.butylamino)-2-hydroxy-propoxy)benzonitrile HCl) (bunitro-lol);

((±)-2'-[3-(tert-butylamino)-2-hydroxypropoxy-5'-fluorobutyrophenone) (butofilolol);

(1-(carbazol-4-yloxy)-3-(isopropylamino)-2-propanol) (carazolol); (5-(3-tert.butylamino-2-hydroxy)propoxy-3,4-dihydrocarbotyril HCl) (carteolol);

(1-(tert.butylamino)-3-(2,5-dichlorophenoxy)-2-propanol) (clorano-lol);

(1-(inden-4(or 7)-yloxy)-3-(isopropylamino)-2-propanol HCl) (indeno-lol);

(1-isopropylamino-3-[(2-methylindol-4-yl)oxy]-2-propanol) (me-pindo-lol);

(1-(4-acetoxy-2,3,5-trimethylphenoxy)-3-isopropylaminopropan-2-ol) (metipranolol);

(1-(isopropylamino)-3-(o-methoxyphenoxy)-3-[(1-methylethyl)amino]-2-propanol) (moprolol);

((1-tert.butylamino)-3-[(5,6,7,8-tetrahydro-cis-6,7-dihydroxy-1-naphthyl)oxy]-2-propanol) (nadolol);

((S)-1-(2-cyclopentylphenoxy)-3-[(1,1-dimethylethyl)amino]-2-propanol sulfate (2:1)) (penbutolol);

(4'-[1-hydroxy-2-(amino)ethyl]methanesulfonanilide) (sotalol);

(2-methyl-3-[4-(2-hydroxy-3-tert.butylaminopropoxy)phenyl]-7-methoxy-isoquinolin-1-(2H)-one);

(1-(4-(2-(4-fluorophenyloxy)ethoxy)phenoxy)-3-isopropylamino-2-propanol HCl);

((-)-p-[3-[(3,4-dimethoxyphenethyl)amino]-2-hydroxypropoxy]-β-methyl-cinnamonitrile) (pacrinolol);

((±)-2-(3'-tert.butylamino-2'-hydroxypropylthio)-4-(5'-carbamoyl-2'-thienyl)thiazole HCl) (arotinolol);

((±)-1-[p-[2-(cyclopropylmethoxy)ethoxy]phenoxy]-3-(isopropyl-amino)-2-propanol) (cicloprolol);

((±)-1-[(3-chloro-2-methylindol-4-yl)oxy]-3-[(2-phenoxyethyl)-amino]-2-propanol) (indopanolol);

((±)-6-[[2-[[3-(p-butoxyphenoxy)-2-hydroxypropyl]amino]ethyl]-amino]-1,3-dimethyluracil) (pirepolol);

(4-(cyclohexylamino)-1-(1-naphtholenyloxy)-2-butanol);

(1-phenyl-3-[2-[3-(2-cyanophenoxy)-2-hydroxypropyl]aminoethyl]-hydantoin HCl);

(3,4-dihydro-8-(2-hydroxy-3-isopropylaminopropoxy)-3-nitroxy-2H-1-benzopyran) (nipradolol);

Angiotensin I Converting Enzyme Inhibitors:

1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline (captopril);

(1-(4-ethoxycarbonyl-2,4(R,R)-dimethylbutanoyl)indoline-2(S)-car-boxylic acid);

(2-[2-[(1-(ethoxycarbonyl)-3-phenyl-propyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid);

((S)-1-[2-[(1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid HCl);

(N-cyclopentyl-N-(3-(2,2-dimethyl-1-oxopropyl)thiol-2-methyl-1-oxo-propyl)glycine) (pivalopril);

((2R,4R)-2-(2-hydroxyphenyl)-3-(3-mercaptopropionyl)-4-thiazolidine-carboxylic acid);

(1-(N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-alanyl)-cis, syn-octa-hydroindol-2(S)-carboxylic acid HCl);

((-)-(S)-1-[(S)-3-mercapto-2-methyl-1-oxopropyl]indoline-2-carboxylic acid);

([1(S),4S]-1-[3-(benzoylthio)-2-methyl-1-oxopropyl]-4-phenylthio-L-proline;

(3-([1-ethoxycarbonyl-3-phenyl-(1S)-propyl]amino)-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1-acetic acid HCl);

(N-(2-benzyl-3-mercaptopropanoyl)-S-ethyl-L-cysteine) and the S-methyl analogue;

(N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline maleate) (enalapril);

N-[1-(S)-carboxy-3-phenylpropyl]-L-alanyl-1-proline;

N^2-[1-(S)-carboxy-3-phenylpropyl]-L-lysyl-L-proline (lysinopril);

Other anti-hypertensive agents: aminophylline; cryptenamine acetates and tannates; deserpidine; meremethoxylline procaine; pargyline; tri-methaphan camsylate; and the like, as well as admixtures and combinations thereof.

Typically, the individual daily dosages for these combinations can range from about one-fifth of the minimally recommended clinical dosages to the maximum recommended levels for the entities when they are given singly. Co-administration is most readily accomplished by combining the active ingredients into a suitable unit dosage form containing the proper dosages of each. Other methods of co-administration are, of course, possible.

The compounds of the present invention are prepared as depicted in the charts and as described more fully in the Preparations and Examples. In the charts, Ph is used to represent the phenyl ring.

Charts A, B, C and D illustrate the preparation of compounds of this invention wherein aspartic or glutamic acid residues are used as

the P2 replacement in renin inhibitory peptides.

Chart A

In step (a) a Nα-Boc protected form of amino acid alcohol such as ch-val-alcohol acid derivative is coupled with a derivative amino acid utilizing standard coupling procedures to yield peptide A-1. In step (b) the N^{α}-Boc moiety is then removed by reacting a solution of A-1 in diethyl ether with HCL gas to yield the peptide A-2. In step (c) A-2 is coupled with a derivative amino acid utilizing diisopropylethyl amine and DEPC to give peptide A-3. In step (d) the peptide A-3 the Nα alpha-Boc moiety is removed utilizing trifluroacetic acid to yield the free amine A-4. In step (e) the amine A-4 is converted to peptide A-5 by reacting it with an appropriately substituted carboxylic acid in the presence of diisopropylethyl amine and DEPC. In step (f) a suspension of peptide A-5 in a solvent, for example, demethylformamide, is reacted with palladium on carbon and ammonium formate to yield the desired compound A-6.

Chart B

In step (a) a Nα-Boc protected form of an amino acid alcohol, such as cha-val-alcohol is coupled with a simple amine utilizing standard coupling procedures to yield peptide B-1 wherein Mba is methylbutyl-amine. In step (b) the N^{α}-Boc moiety is then removed by reacting a solution of B-1 in diethyl ether with HCL gas to yield the peptide B-2. In step (c) B-2 is coupled with a derivative aspartic or glutamic acid utilizing diisopropylethyl amine and DEPC to give peptide B-3. In step (d) the benzyl moiety of peptide B-3 is removed by contacting the peptide with hydrogen in the presence of a palladium/carbon catalyst to yield compound B-4.

Chart C

In step (a) Nα-Boc protected aspartic or glutamic acid derivative is coupled with leu-val-alcohol-containing fragment utilizing standard coupling procedures to yield peptide C-1. In step (b) the N^{α}-Boc moiety is removed by reacting a solution of C-1 in dichloromethane with triflouroacetic acid yield the peptide C-2. In step (c) C-2 is coupled with a substituted acetic acid utilizing diisopropylethyl amine and DEPC to give peptide C-3. In step (d) the acid protecting group is removed by contacting a solution of C-3 in a solvent, such as di-methylformamide, with palladium on carbon and ammonium formate to yield C-4.

CHART D

Chart D illustrates a process that is similar to the one illustrated in Chart C. Different amine is coupled in step (a) and that removal of the benzy group in step (d) is accomplished by the use of hydrogen gas rather than ammonium formate.

CHART E

Chart E illustrates the preparation of compounds wherein malic acid residues are used as a P_2(subscript) replacement in renin inhibitory peptide.

In step (a) amide E-1 is reacted with trifluoracetic acid to yield the free amine E-2. Amides of the type exemplified by E-1 are commercially available or can be made by methods well known in the art. For example by the method of step (b) of Chart B. In step (b) E-2 is then reacted with benzyl S-malate in the presence of diisopropyl ethyl amine and DEPC to yield the alcohol E-3. In step (c) the alcohol E-3 is converted to peptide E-4 by reacting it with the appropriately substituted acyl chloride in the presence of DMAP. In step (d) peptide E-4 is deprotected to yield peptide E-5. In step (e) peptide E-5 is deesterified by reacting it with hydrogen, carbon and ammonium formate to yield the compound E-6.

The individual steps illustrated in the charts are procedures that are well known in the art. Also, the starting materials are readily available or can be made by methods well known in the art.

The derivative amino acids are incorporated into a peptide using standard coupling procedures. Should the peptide exist in a protected form, the protecting groups are removed prior to coupling. For example, a Boc group is removed from an N-terminus with trifluoroacetic acid in methylene chloride and then the derivative acid is introduced. After coupling, any remaining protecting groups are removed under standard conditions. For example a tosyl group is removed from histidine using 1-hydroxybenzotriazole in methanol.

Generally, the renin inhibiting polypeptides may be prepared by either polymer assisted or solution phase peptide synthetic procedures analogous to those described hereinafter or to those methods known in the art. For example, the carboxylic moiety of N^{α}-t-butyloxycarbonyl (Boc)-substituted amino acid derivatives having suitable side chain protecting groups, if necessary, may be condensed with the amino functionality of a suitably protected amino acid, peptide or polymer-

bound peptide using a conventional coupling protocol such as dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) or diethylphosphoryl cyanide (DEPC) and triethylamine (Et_3N) in methylene chloride or dimethylformamide. The synthetic procedures used to incorporate the novel moieties herein are analogous to those described, for example, in U.S. patents 4,424,207; 4,470,971; 4,477,440; 4,477,441; 4,478,826; 4,478,827; 4,479,941; and 4,485,099, and co-pending application Serial No. 753,198 filed 9 July 1985, and co-pending application Serial No. 825,250 filed 3 February 1986, all of which are expressly incorporated by reference herein. See, also, published European patent applications 45,161; 45,665; 53,017; 77,028; 77,029; 81,783; 104,041; 111,266; 114,993; and 118,223.

Following coupling reaction completion, the N^{α}-Boc moiety may be selectively removed with 45% trifluoroacetic acid with or without 2% anisole (v/v) in methylene chloride. Neutralization of the resultant trifluoroacetate salt may be accomplished with 10% diisopropylethylamine or sodium bicarbonate in methylene chloride. In the case of polymer-assisted peptide synthesis, this stepwise, coupling strategy may be partially or completely automated to provide the desired peptide-polymer intermediates. Anhydrous hydrofluoric acid treatment of the peptide-polymer intermediate may then be used to effect simultaneous protecting group removal and cleavage of the peptide from its polymeric support. A notable exception to this includes N^{in}-formyl-indolyl-substituted peptides in which the N^{in}-formyl-indolyl moiety is stable to TFA or HF but may be removed by NH_3 or NaOH. Because FTrp is somewhat unstable to base in synthetic procedures, possibly causing lower yields, it may be desirable in solution phase synthesis to introduce the FTrp-containing moiety late in the synthetic sequence so that it is not exposed to such conditions.

The incorporation of N^{in}-formyl-Trp into compounds of the present invention is easily accomplished because of the commercial availability of N^{α}-Boc-N^{in}-formyl-Trp-OH. However, the N^{in}-formyl moiety may be introduced into indolyl-substituted amino acid derivatives or related compounds by reaction with HCl-formic acid as reported in the literature, see A. Previero et al, Biochim. Biophys. Acta 147, 453 (1967); Y.C.S. Yang et al, Int. J. Peptide Protein Res. 15, 130 (1980).

Generally, methods of alkylation useful in alkylating histidine for use in the present invention are found in Cheung, S.T. et al,

Can. J. Chem., Vol 55, pp. 906-910 (1977). However, it is now found that in Cheung, S.T. et al. methods it is critical that the reaction conditions for the alkylation of histidine be anhydrous. Further, it is now found also that during work-up instead of adding water directly to the reaction mixture, it is preferred that a buffered aqueous solution be added to the reaction mixture, for example, aqueous sodium or potassium hydrogen sulfate.

Variations in the above description for starting materials, reactants, reaction conditions and required protecting groups to obtain other such N-alkylated compounds are known to an ordinarily skilled chemist or are readily available in the literature.

These peptides may also be prepared by the standard solid phase techniques of Merrifield. Appropriate protecting groups, reagents, and solvents for both the solution and solid phase methods can be found in "The Peptides: Analysis, Synthesis, and Biology," Vols. 1-5, eds. E. Gross and T. Meienhofer, Academic Press, NY, 1979-1983.

The compounds of the present invention may be in either free form or in protected form at one or more of the remaining (not previously protected) peptide, carboxyl, amino, hydroxy, or other reactive groups. The protecting groups may be any of those known in the polypeptide art. Examples of nitrogen and oxygen protection groups are set forth in T.W. Greene, Protecting Groups in Organic Synthesis, Wiley, New York, (1981); J.F.W. McOmie, ed. Protective Groups in Organic Chemistry, Plenum Press (1973); and J. Fuhrhop and G. Benzlin, Organic Synthesis, Verlag Chemie (1983). Included among the nitrogen protective groups are t-butoxycarbonyl (Boc), benzyloxycarbonyl, acetyl, allyl, phthalyl, benzyl, benzoyl, trityl and the like.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following Preparations and Examples illustrate the present invention.

In the Preparations and Examples below and throughout this document:

Ac is acetyl;

AMP is 2-(aminomethyl)pyridine;

BOC is t-butoxycarbonyl;

BOM is benzyloxymethyl;

Bz is benzyl;

C is centigrade;

Celite is a filter aid;

DCC is dicyclohexylcarbodiimide;

DEPCis diethylcyanophosphate;

DMAP is dimethylaminopyridine;

DMF is dimethylformamide;

EtOAc is ethyl acetate;

g. is grams;

HPLC is high performance liquid chromatography;

I_2 is iodine;

IR is infra red spectra;

A Lindlar catalyst is a modified 5% palladium on calcium carbonate catalyst, obtained from Engelhard Industries and used for reduction;

M or mol is mole;

MBA is 2-methylbutylamino (racemic or optically active);

MBAS is 2S-methylbutylamino;

Me is methyl;

min. is minute;

ml is milliliter;

MS is mass spectroscopy;

NMHis is Nα-methyl-L-histidine;

NMR is nuclear magnetic resonance;

NOAl is (1-naphthyloxy)acetyl;

p-TSA salt is para-toluene sulfonic acid salt;

Ph is phenyl;

POA is phenoxyacetyl;

RIP means a compound having the formula H-Pro-His-Phe-His-Phe-Phe-Val-Tyr-Lys-OH.2($CH_3C(O)OH$).XH_2O which is a known renin-inhibiting peptide.

Skellysolve B is as defined in the Merck Index, 10th edition;

TBDMS is t-butyldimethylsilyl;

TFA is trifluoroacetic acid;

THF is tetrahydrofuran;

TLC is thin layer chromatography;

Tos is p-toluenesulfonyl;

Tr is trityl (triphenylmethyl);

2HPA is (±)-(2-hydroxypropyl)amino; and

UV is ultraviolet.

The wedge-shape line indicates a bond which extends above the

plane of the paper relative to the plane of the compound thereon.

The dotted line indicates a bond which extends below the plane of the paper relative to the plane of the compound thereon.

Preferred compounds are those of Formula IC in which the aspartic acid residue has been used as a replacement in the renin inhibiting peptide and the stereochemistry at the 2, 4, and 5 carbon atoms of the transition state insert is of the S configuration. The compound 3-S-phenylacetylamino-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-6-(cyclohexylmethylhexanoyl-L-isoleucyl-2-pyridylmethylamide and its use as a renin inhibitor represents among the best mode contemplated by the applicants to practice the invention.

Example 1

(2S-Phenylacetylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-6-cyclohexylmethyl-hexanoyl-L-isoleucyl-2-pyridylmethyl amide. (Refer to Chart A)

(a) To a stirred solution of 100.6 mg (0.027 mmol) of Nα-5S-tert-Butyloxycarbonyl)-4S-tert-butyldimethylsilyloxy-2S-isopropyl-6-cyclohexymethyl-hexanoic acid A and 54.9 mg (0.248 mmol) of Ile-Amp in 1.0 mL of dry dichloromethane was added 60 µl (0.331 mmol) of diisopropylethyl amine followed by 45 µl (0.289 mmol) of diethylcyanophosphonate. After 4 hours at room temperature, the concentrated reaction mixture was chromatographed on 15 g of silica gel using 50% to 70% ethyl acetate in dichloromethane to afford 135.1 mg (0.195 mmol, 95%) of desired peptide Nα-5S-tert-Butyloxycarbonyl)-4S-tert-butyldimethylsilyloxy-2S-isopropyl-6-cyclohexymethyl-hexanoyl-L-isoleucyl-2-pyridylmethyl amide.

(b) To a stirred solution of 135.1 mg (0.195 mmol) of the product prepared in step (a) in 10 mL of dry ether was passed over the surface dry HCl gas until saturated. After 25 minutes, the ether was removed via a stream of argon and then pumped on high vac for 2 hours to afford the amine A-2 as a white ppt.

(c) To this residue and 80.7 mg (0.249 mmol) of Boc-L-aspartic-α-benzyl ester in 1.5 ml of dichloromethane was added 0.15 mL (0.877 mmol) of diisopropylethyl amine followed by 50 µl (0.312 mmol) of diethylcyanophosphonate. After 3 hours at room temperature, the concentrated mixture was chromatographed on 18 g of silica gel using 5% methanol in dichloromethane to afford 133.7 mg (0.171 mmol, 88%) of the peptide 2S-tert-Butyloxycarbonylamino-1-benzyl-succinyl-5S-amino-4S-

hydroxyl-2S-isopropyl-6-cyclohexylmethyl-hexanoyl-L-isoleucyl-2-pyridylmethyl amide.

(d) A stirred solution of 133.2 mg (0.170 mmol) of the peptide prepared in step (c) in 1.0 mL of dichloromethane and 1.0 mL of trifluoroacetic acid was stirred at room temperature for 45 min. The reaction mixture was slowly added to 1.5 g of $NaHCO_3$ in 15 mL of water. The aqueous phase was extracted with dichloromethane. The combined organics were dried ($MgSO_4$) and concentrated to afford 111.7 mg (0.164 mmol, 97%) of desired free amine 2S-amino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-6-cyclohexylmethyhexanoyl-L-isoleucyl-2-pyridylmethyl amide.

(e) To a stirred solution of 55.0 mg (0.080 mmol) of the amine prepared in step (d) and 14.3 mg (0.105 mmol) of phenyl acetic acid in 0.8 mL of dichloromethane was added 30 μl (0.169 mmol) of diisopropylethyl amine followed by 20 μl (0.129 mmol) of diethylcyanophosphonate. After 2 hours, the concentrated mixture was chromatographed on 8 g of silica gel using 3% to 5% methanol in dichloromethane to afford 56 mg (0.070 mmol, 88%) of the peptide 2S-Phenylacetylamino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-6-cyclohexyl-methyl-hexanoyl-L-isoleucyl-2-pyridylmethyl amine.

(f) To a stirred suspension of 56 mg of the peptide prepared in step (e) in 1 mL of dimethylformamide was added 30 mg of 10% palladium on carbon, followed by 60 mg of ammonium formate. After 5 hours, the mixture was diluted with methanol and then filtered through celite with methanol washings. The filtrate was concentrated and dried in vacuo overnight to afford 45 mg of (2S-Phenylacetylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-6-cyclohexylmethyl-hexanoyl-L-isoleucyl-2-pyridylmethyl amide. FAB HRMS: $[M + H]^+$ at m/z = 708.4328 (cal'd for 708.4336).

Example 2

3S-Phenoxyacetylamino-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-6-cyclohexylmethy-hexanoyl-L-isoleucyl-2-pyridylmethyl amide. (Refer to Chart A)

(e) To a stirred solution of 56.6 mg (0.083 mmol) of the amine prepared in step (d) of Example and 16.4 mg (0.108 mmol) of phenoxyacetic acid in 0.8 mL of dichloromethane was added 30 μl (0.174 mmol) of diisopropylethyl amine followed by 20 μl (0.133 mmol) of diethylcyanophosphonate. After a few hours, the concentrated reaction mixture

was chromatographed on silica gel using 3% to 5% methanol in dichloromethane to afford 65 mg (0.079 mmol, 96%) of peptide 2S-Phenoxyacetylamino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isoproypyl-6-cyclohexylmethyl-hexanoyl-L-isoleucyl-2-pyridylmethyl amine.

(f) To a stirred suspension of 65 mg of the amine prepared in step (e) in 1 mL of dimethylformamide was added 30 mg of 10% palladium on carbon, followed by 60 mg of ammonium formate. After 5 hours, the mixture was diluted with methanol and then filtered through celite with methanol washings. The filtrate was concentrated and dried in vacuo overnight to afford 55 mg of 2S-Phenoxyacetylamino-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-6-cyclohexylmethy-hexanoyl-L-isoleucyl-2-pyridylmethyl amide.

GAB HRMS: [M + H] = at m/Z = 724.4339 (cal'd for 724.4363).

Example 3

Phenylacetyl-β-L-aspartyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-2S-methylbutylamide (Refer to Chart B)

(a) To a stirred solution of 42.4 mg (87.3 μmol) of Nα-5S-tert-Butyloxycarbonyl)-4S-butyldimethylsilyloxy-2S-isopropyl-6-cyclohexymethyl-hexanoic acid A and 11 μl (97 μmol) of 2S-methylbutylamine in 0.5 mL of CH_2Cl_2 was added 17 μL (97 μmol) of diisopropylethylamine and 15 μL (98 μmol) of DEPC. After 18 hours, the reaction mixture was flashed on silica with 20% ETOAc-hexane to afford 41.4 mg (86%) of O-tert-Butyldimethylsilyl-N-tert-butyloxycarbonyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-2S-methylbutylamide 9. 1H NMR ($CDCl_3$) δ .08 (s), .09 (s) 0.8-1.0 (m), 1.0-1.9 (m), 1.46 (s), 2.9-3.0 (m), 3.1-3.2 (m), 3.6-3.8 (m), 4.5 (d), 5.8 (m), FAB MS $(m + H)^+$ = 555.4551; cal'd 555.4557.

(b) A solution of 845 mg (2.61 mmol) of Boc-Asp-α-OBn in 15 ml dry ether was saturated with dry HCl. After 30 minutes, volatiles were removed under a gentle stream of N_2, and the residue pumped via a KOH trap.

To the residue was sequentially added 8 ml water, 500 mg (4.7 mmol) of Na_2CO_3 and 0.34 ml of phenylacetyl chloride. The heterogeneous mixture was stirred vigorously for 2 hours, after which it was nearly clear. Acidification of the solution was 6N HCl produced a white precipitate, which was extracted with 4 portions of CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give an oil, which contained the desired product along with about

20% phenylacetic acid (by NMR integration). Chromatography of the oil on silica with 4-8-12% MeOH-CH_2Cl_2 provided a clean sample of N-phenacetyl aspartic acid α-benzyl ester B, albeit with poor recovery. For B: 1H NMR ($CDCl_3$) δ 2.92 (dd, J_1 = 4.5 Hz, J_2 = 49 Hz, 1H); 2.97 (dd, J_1 = 4.5 Hz, J_2 = 49 Hz, 1 H); 3.59 (2, 2 H); 4.89 (dt, 1 H); 5.10 (dd, 2 H); 6.61 (d, 1 H), 7.2-7.4 (m, 10 H).

(c) A solution of 40.4 mg (72.8 μmol) of compound B-I in 8 ml of dry ether was saturated with dry HCl. After 30 min, volatiles were removed under a gentle stream of N_2, and the residue pumped via a KOH trap.

(d) To this residue was sequentially added N-phenylacetyl-α-benzyl-L-aspartic acid (30 mg, 88 μmol), 0.5 ml of CH_2Cl_2, 41 μL (0.24 mmol) of diisopropylethylamine, and 13 μL (85 μmol) of DEPC. After 18 hours, the mixture was chromatographed on silica with 2-3% MeOH-CH_2Cl_2 to afford 41.5 mg (86%) of phenylacetyl-α-benzyl-L-aspartyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-2S-methylbutylamide. 1H NMR ($CDCl_3$) δ 0.7-1.9 (m), 2.0-2.1 (m), 2.6-2.9 (2 x dd), 3.58 (s), 4.8 (dt), 5.2 (dd), 6.7 (m), 6.9 (d), 7.2-7.4 (m), 7.5 (d). FAB MS $(m + H)^+$ = 664.4317; cal'd 664.4325

(e) A mixture of 41 mg (62 μmol) of the peptide prepared in step (b) and a catalytic amount of 10% Pd/C in a small amount of MeOH (containing a little Ch_2Cl_2 to aid peptide solubility) was stirred vigorously under 1 atm. H_2 for 2 1/2 hours, then filtered through a pad of celite. The residue remaining after concentration of the filtrate was chromatographed on silica with 5-15% MeOH-CH_2Cl_2 to afford 16.4 mg of phenylacetyl-β-L-aspartyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-2S-methylbutylamide. Because the product did not show up well under UV or stain with I_2 or with vannilin, PMA, or ninhydrin TLC sprays, chromatography fractions were assayed by HPLC. 1H NHR ($COCl_3$) δ 0.7-1.9 (m), 2.1-2.2 (m), 2.6-3.9 (m), 4.5-4.6 (m), 7.1-7.4 (m). FAB MS $(m + H)^+$ = 574.

Example 4

Phenylacetyl-β-L-aspartyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoylmethylamide (Refer to Chart B)

(a) To a stirred solution of 77.5 mg (0.16 mmol) of Nα-5S-tert-Butyloxycarbonyl)-4S-tert-butyldimethylsilyloxy-2S-isopropyl-6-cyclohexymethyl-hexanoic acid and 22 mg (.033 mmol) of methylammonium chloride in 1 ml. of CH_2Cl_2 was added 83 μl (0.48 mmol) of diisopro-

pylethylamine and 30 μL (0.20 mmol) of DEPC. After 18 hours the mixture was flashed on silica with 20% ETOAc-CH_2Cl_2 to provide 77.0 mg (97%) of O-tert-Butyldimethylsilyl-N-tert-butyloxycarbonyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-methylamide.

1H NMR ($CDCl_3$) δ 0.08 (s), 0.09 (s) .82 (s), 0.8-1.8 (m), 1.37 (s), 2.64 (d), 3.5-3.8 (m), 4.4 (d), 5.8 (m). FAB MS $(m + H)^+$ = 499.3910; cal'd 499.3931

(b) A solution of 845 mg (2.61 mmol) of Boc-Asp-α-OBn in 15 ml dry ether was saturated with dry HCl. After 30 minutes, volatiles were removed under a gentle stream of N_2, and the residue pumped via a KOH trap.

To the residue was sequentially added 8 ml water, 500 mg (4.7 mmol) of Na_2CO_3, and 0.34 ml of phenylacetyl chloride. The heterogeneous mixture was stirred vigorously for 2 hours, after which it was nearly clear. Acidification of the solution was 6N HCl produced a white precipitate, which was extracted with four portions of CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give an oil, which contained the desired product along with about 20% phenylacetic acid (by NMR integration). Chromatography of the oil on silica with 4-8-12% MeOH-CH_2Cl_2 provided a clean sample of N-phenacetyl aspartic acid α-benzyl ester B, albeit with poor recovery. For B: 1H NMR ($CDCl_3$) δ 2.92 (dd, J_1 = 4.5 Hz, J_2 = 49 Hz, 1H); 2.97 (dd, J_1 = 4.5 Hz, J_2 = 49 Hz, 1 H); 3.59 (2, 2 H); 4.89 (dt, 1 H); 5.10 (dd, 2 H); 6.61 (d, 1 H), 7.2-7.4 (m, 10 H).

(c) A solution of 76 mg (0.15 mmol) of the peptide prepared in step (a) in 8 ml dry ether was saturated with dry HCl. After 20 minutes, volatiles were removed under a gentle stream of N_2 and the residue pumped via a KOH trap.

(d) Twenty-eight milligrams (90 μmol) of this residue and 40 mg (0.12 mmol) of phenacetyl aspartic acid benzyl ester B were dissolved in 0.9 ml of CH_2Cl_2, and to this stirred solution was added 39 μmol (0.22 mmol) of diisopropylethylamine and 18 μL (.12 mmol) of DEPC. After 18 hours the reaction mixture was chromatographed on silica with 2-4% MeOH-CH_2Cl_2 to afford 43.3 mg (79%) of phenylacetyl-α-benzyl-L-aspartyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl methylamide.

1H NMR ($CDCl_3$) δ 0.7-2.1 (m), 2.6-2.9 (2 x dd), 2.8 (d), 3.3-3.8 (m), 4.8 (m), 5.1 (dd), 6.9-7.1 (m), 7.2-7.4 (m); 7.7 (d). FAB MS (m +

$H)^+$ = 608.3686; cal'd 608.3699

(e) A mixture of 43 mg (71 μmol) of the peptide prepared in step (d) and a catalytic amount of 10% Pd-C in a small amount of MeOH (containing a little CH_2Cl_2 for peptide solubility) was stirred vigorously under 1 atm. H_2 for two hours. The mixture was filtered through celite and the filtrate concentrated under reduced pressure to afford 37 mg (100%) of phenylacetyl-β-L-aspartyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoylmethylamide.

FAB MS $(m + H)_+$ = 518.3245; cal'd 518.3230.

Example 5

2S-Phenylacetylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethyl amide (Refer to Chart C)

(a) To a stirred solution of 157.0 mg (0.485 mmol) of Boc-L-aspartic acid-α-benzyl ester and 295.7 mg (0.582 mmol) of LVA-IIe-Amp.2HCl in 2.0 mL of dichloromethane was added 0.36 mL (2.03 mmol) of diisopropylethylamine followed by 0.10 mL (0.631 mmol) of diethylcyanophosphonate. After 10 minutes, reaction mixture was a gel. The reaction mixture was agitated at room temperature overnight. Partitioned between dicholoromethane and saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane. Combined organics were dried (MgSO4), filtered and concentrated. The residue was chromatographed on 35 g of silica gel (very difficult loading) using 5% methanol in dichloromethane to afford 332.3 mg (0.450 mmol, 93%) of desired peptide 2S-tert-Butyloxycarbonyl-amino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethyl amide. FAB HRMS: $[M + H]^+$ at m/Z = 740.4616 (cal'd for 740.4598).

(b) To a stirred solution of 747.5 mg (1.01 mmol) of the peptide prepared in step (a) A in 2.0 mL of dichloromethane was added 2.0 mL of trifluoroacetic acid. After 45 minutes at room temperature, the reaction mixture was slowly pipetted into a stirred solution containing 3.0 g of $NaHCO_3$ in 30 mL of water. After 10 minutes, the phases were separated. The aqueous phase was extracted with four portions of dichloromethane. The combined organics were dried ($MgSO_4$), filtered and concentrated to afford 641.3 mg (1.00 mmol) of the desired free amine 2S-amino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethyl amide.

(c) To a stirred solution of 425.6 mg (0.666 mmol) of the amine

prepared in step (b) and 117.8 mg of phenylacetic acid in 3 ml. of dichloromethane was added 0.24 mL (1.39 mmol) of diisopropylethyl amine followed by 0.16 mL (1.06 mmol) of diethylcyanophosphonate. After 10 minutes, reaction mixture was a gel. The reaction mixture was agitated at room temperature overnight. Partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane. Combined organics were dried with magnesium sulfate, filtered, and concentrated. The residue was chromatographed on 50 g of silica gel (very difficult loading) using 3% to 5% methanol in dichloromethane to afford 322.6 mg (0.426 mmol, 65%) of the peptide 2S-phenylacetylamino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2s-isopropyl-7-methyloctanyl-L-isoleucyl-2-pyridylmethyl amide. FAB HRMS: [M + H] + at m/Z = 758.4505 (cal'd for 758.4492).

(d) To a stirred suspension of 120.1 mg (0.158 mmol) of the peptide prepared in step (c) in dimethylformanide was added 75 mg of 10% palladium on carbon followed by 109.5 mg (1.73 mmol) of ammonium formate. The reaction mixture was stirred for 3 hours at room temperature, then diluted with methanol. The reaction mixture was filtered through celite, catalyst washed with methanol, and the filtrate was concentrated. The residue was chromatographed on silica gel using 20% methanol in dichloromethane to afford 120 mg of 2S-phenylacetylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethyl amide. FAR HRMS: $[M + H]^+$ at m/Z = 668.4062 (cal'd for 668.4023).

Example 6

(2S-Phenoxyacetylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethyl amide (Refer to Chart C)

Steps (a) and (b) were the same as steps (a) and (b) of Example 5.

(c) To a stirred solution of 78.5 mg (0.122 mmol) of 2S-amino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethyl amide prepared in step (c) and 22.4 mg (0.147 mmol) of phenoxyacetic acid in 0.6 mL of dichloromethane was added 39 μL (0.221 mmol) of diisopropylethylamine followed by 25 μL (0.172 mmol) of diethylcyanophosphonate. After 10 minutes, reaction mixture was a gel. The reaction mixture was agitated at room temperature for 5 hours. The reaction mixture was diluted with dichloromethane and some methanol, then concentrated. The residue was chromatographed on 15 g of silica gel using 3% to 5% methanol in dichloromethane to afford 67.5

mg (0.087 mmol, 72%) of peptide 2S-phenoxyacetylamino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethyl amide.

FAB HRMS: $[M + H]^+$ at m/Z = 774.4474 (cal'd for 773.4442).

(d) To a stirred suspension of 31.5 mg (0.040 mmol) of the peptide prepared in step (c) in dimetyylformamide was added 17 mg of 10% palladium on carbon followed by 28.2 mg (0.448 mmol) of ammonium formate. The reaction mixture was stirred for three hours at room temperature, then diluted with methanol. The reaction mixture was filtered through celite, catalyst washed with methanol, and the filtrate was concentrated. The residue was chromatographed on silica gel using 20% methanol in dichloromethane to afford 23.4 mg of (2S-phenoxyacetylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethyl amide. FAB HRMS: [M + H]- at m/Z = 706.3811 (cal'd for $C_{36}H_{53}N_5O_3Na$ = 706.3992).

Example 7

(2S-Benzoylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoly-L-isoleucyl-2-pyridylmethylamide (Refer to Chart C)

Steps (a) and (b) were the same as in Examples 5 and 6.

(c) To a stirred solution of 73.8 mg (0.115 mmol) of the amine prepared in step (b) and 16.9 mg mg (0.138 mmol) of benzoic acid in 0.6 mL of dichloromethane was added 30 μl (0.173 mmol) of diisopropylethyl amine followed by 25 μl (0.161 mmol) of diethylcyanophosphonate. After 10 minutes, reaction mixture was a gel. The reaction mixture was agitated at room temperature for five hours. Partitioned between dichloromethane and saturated aqueous $NaHCO_3$. The aqueous phase was extracted with dichloromethane. Combined organics were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on 14 g of silica gel using 3 to 5% methanol in dichloromethane to afford 65.6 mg (0.088 mmol, 77%) of desired peptide (2S-benzoylamino-1-benzylsuccinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethyl amide.

FAB HRMS: $[M + H]^+$ at m/Z = 744.4313 (cal'd for 744.4336).

(d) To a stirred suspension of 28.5 mg. (0.038 mmol) of the peptide prepared in step (c) in dimethylformamide was added 11 mg. of 10% palladium on carbon followed by 26.5 mg. (0.421 mmol) of ammonium formate. The reaction mixture was stirred for three hours at room temperature, then diluted with methanol. The reaction mixture was

filtered through celite, catalyst washed with methanol, and the filtrate was concentrated to afford 24.2 mg. (0.037 mmol, 97%) of (2S-benzoylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoly-L-isoleucyl-2-pyridylmethylamide. FAB HRMS $[M + H]^+$ at m/Z = 654.3902 (cal'd for 654.3866).

Example 8

[2S-(2-Pyridinyl)acetylamino]-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide (Refer to Chart C)

Steps (a) and (b) were the same as in Examples 5, 6 and 7.

(c) To a stirred solution of 72.6 mg. (0.113 mmol) of the amine prepared step (b) in and 25.6 mg. (0.147 mmol) of 2-pyridinylacetic acid in 0.6 ml. of dichloromethane was added 60 µl (0.341 mmol) of diisopropylethylamine followed by 30 µl (0.191 mmol) of diethyl-cyanophosphonate. After 10 minutes, reaction mixture was a gel. The reaction mixture was agitated at room temperature overnight. The reaction mixture was diluted with dichloromethane and some methanol and then concentrated. The residue was chromatographed on 14 g. of silica gel using 3% to 5% methanol in dichloromethane to afford 84 mg. of the peptide 2S-(2-pyridinyl)acetylamino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethyl-amide. FAB HRMS: $[M - H]^+$ at m/Z = 759.4445 (cal'd for 759.4445).

(d) To a stirred solution of 42.0 mg. (0.055 mmol) of the peptide prepared in step (c), in 0.3 ml. of glacial acetic acid was added 42.0 mg. of 10% palladium on carbon followed by 100 µl of 1,4-cyclohexyl-diene. The reaction mixture was stirred at room temperature for 18 hours, then filtered through celite. Catalyst washed with 1:1 acetic acid/methanol. The filtrate was concentrated to afford 28.0 mg. (0.042 mmol, 75%) of [2S-(2-Pyridinyl)acetylamino]-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethyl-amide. FAB HRSM: $[M + H]^+$ at m/Z = 669.3998 (cal'd for 669.3975).

Example 9

[2S-(3-Pyridinyl)acetylamino]-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide (Refer to Chart C)

Steps (a) and (b) were the same as in Examples 5 thru 8.

(c) To a stirred solution of 69.3 mg. (0.018 mmol) of the amine prepared in step (b) and 24.5 mg. (0.141 mmol) of 3-pyridylacetic

acid·HCl in 0.5 ml. of dichloromethane was added 57 μl (0,325 mmol) of diisopropylethylamine followed by 26 μl (0.173 mmol) of diethylcyanophosphonate. After 10 minutes, the reaction mixture was a gel. The reaction mixture was agitated at room temperature overnight. Diluted with dichloromethane and some methanol and then concentrated. The residue was chromatographed on 10 g. of silica gel using 4% to 5% to 6% methanol in dichloromethane to afford 77.0 mg. (0.101 mmol, 94%) of the peptide 2S-(3-pyridinyl)acetylamino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide). FAB HRMS: $[M - H)^+$ at m/Z = 759.4445 (cal'd for 759.4445).

(d) To a stirred solution of 38.5 mg. (0.050 mmol) of the peptide prepared in step (c) in 0.25 ml. of glacial acetic acid was added 38.5 mg. of 10% palladium on carbon followed by 100 μl of 1,4-cyclohexyldiene. After stirring at room temperature for 20 hours, the mixture was filtered through celite. The catalyst was washed with methanol and the filtrate concentrated. The residue was chromatographed on 4.7 g. of silica gel using 15% to 20% methanol in dichloromethane to afford 12 mg. of [2S-(3-pyridinyl)acetylamino]-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide. FAB HRMS: $[M + H]^+$ at m/Z = 691.3786 (cal'd for 691.3795).

Example 10

(2S-Phenylacetylamino)-glutaryl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide (Refer to Chart C)

(a) To a stirred solution of 98.5 mg. (0.292 mmol) of Boc-L-glutamic acid-α-benzyl ester and 114.1 mg. (0.224 mmol) of LVA-Ile-Amp·2 HCl in 2.0 ml. of dichloromethane was added 0.18 mmol (1.01 mmol) of diisopropylethylamine followed by 55 μl (0.359 mmol) of diethylcyanophosphonate. The reaction mixture was stirred at room temperature for four hours, then concentrated and chromatographed on 19 g. of silica gel using 3% to 5% methanol in dichloromethane to afford 146.5 mg. (0.194 mmol, 87%) of the peptide 2S-tert-butyloxycarbonyl-amino-1-benzyl-glutaryl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide. FAB HRMS: $[M + H)^+$ at m/Z = 754.4772 (calc'd for 754.4755).

(b) To a stirred solution of 146.5 mg. (0.194 mmole) of the peptide prepared in step (a) in 1.0 ml. of dichloromethane was added 1.0 ml. of trifluoroacetic acid. After 45 minutes at room temperature, the reaction mixture was slowly pipetted into a stirred solution of 65

g. of sodium bicarbonate in 15 ml. of water. After 10 minutes, the phases were separated. The aqueous phase was extracted with dichloromethane. The combined organics were dried with magnesium sulfate filtered, and concentrated to afford 103 mg. (0.157 mmol, 82%) of the desired amine.

(c) To a stirred solution of 27.7 mg. (0.204 mmol) of phenyl acetic acid and 103 mg. (0.157 mmol) of the amine prepared in step (b) in 1.5 ml. of dichloromethane was added 60 μl (0.329 mmol) of diisopropylethylamine followed by 40 μl (0.251 mmol) of diethylcyanophosphonate. After 10 minutes, the reaction mixture was a gel. The reaction mixture was agitated at room temperature for 3.5 hours. The reaction mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane. Combined organics were dried with magnesium sulfate, filtered and concentrated. The residue was chromatographed on 12 g. of silica gel using 5% methanol in dichloromethane to afford 68.9 mg. (0.089 mmol, 57%) of peptide 2S-phenylacetylamino-1-benzylglutaryl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide. FAB HRMS: $[M + H]^+$ at m/Z = 772.4657 (cal'd for 772.4649).

(d) To a stirred suspension of 33.4 mg. (0.043 mmol) of the peptide in dimethylformamide was added 15 mg. of 10% palladium on carbon followed by 30.0 mg. (0.476 mmol) of ammonium formate. The reaction mixture was stirred for three hours at room temperature, then diluted with methanol. The reaction mixture was filtered through celite, catalyst washed with methanol and the filtrate was concentrated to afford 28.1 mg. of (2S-phenylacetylamino)-glutaryl-5S-amino-4S-hydroxy-2S-isopropyl-7 methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide. FAB HRMS: $[M + H]^+$ at m/Z = 682.4199 (cal'd for 682.4179).

Example 11

(2S-Phenoxyacetylamino)-glutaryl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide) (Refer to Chart C)

Steps (a) and (b) are the same as in Example 10.

(c) To a stirred solution of 23.2 mg. (0.152 mmol) of phenoxyacetic acid and 76.8 mg. (0.117 mmol) of the amine prepared in step (b) in 1.0 ml. of dichloromethane was added 45 μl (0.246 mmol) of diisopropylethylamine followed by 30 μl (0.188 mmol) of diethylcyanophosphonate. After 10 minutes the reaction mixture was a gel. The reaction mixture was agitated at room temperature four hours, then concentrated. The

residue was chromatographed on 11 g. of silica gel using 5% methanol in dichloromethane to afford 69.6 mg. (0.088 mmol, 76%) of the peptide 2S-phenoxyacetylamino-1-benzylglutaryl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-L-isoelucyl-2-pyridylmethylamide. FAB HMRS: $[M + H]^+$ at m/Z = 788.4614 (cal'd for 788.4598).

(d) To a stirred suspension of 30.8 mg. (0.039 mmol) of the peptide prepared in step (c) in dimethylformamide was added 15 mg. of 10% palladium on carbon followed by 27 mg. (0.430 mmol) of ammonium formate. The reaction mixture was stirred overnight at room temperature, then diluted with methanol. The reaction mixture was filtered through celite, catalyst washed with methanol and the filtrate was concentrated to afford 26 mg. of (2S-Phenoxyacetylamino)-glutaryl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridyl-methylamide. FAB HRMS: $[M + H]^+$ at m/Z = 698.4165 (cal'd for 698.4129).

Example 12

2R-Phenylacetylamino)-succinyul-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanyl-L-isoleucyl-2-pyridylmethylamide (Refer to Chart D)

(a) To a stirred solution of 81.3 mg. (0.251 mmol) of Boc-D-aspartic acid-α-benzyl ester and 98.2 mg. (0.193 mmol) of LVA-Ile-Amp·2HCl in 1.0 ml. of dichloromethane was added 0.15 ml. (0.970 mmol) of diisopropylethylamine followed by 50 μl (0.309 mmol) of diethyl-cyanophosphonate. After 10 minutes the reaction mixture was very dark. The reaction mixture was stirred at room temperature overnight, then concentrated. The residue was chromatographed on 17 g. of silica gel using 5% methanol in dichloromethane to afford 114.8 mg. (0.155 mmol, 80%) of the peptide 2R-tert-Butyloxycarbonyl-amino-1-benzylsuccinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide. FAB HRMS: $[M + H]^+$ at m/Z = 740.4633 (cal'd for 740.4598).

(b) To a stirred solution of 114.8 mg. (0.155 mmol) of the peptide prepared in step a (17) in 1.0 ml. of dichloromethane was added 1.0 ml. of trifluoroacetic acid. After 45 minutes at room temperature, the reaction mixture was slowly pipetted into a stirred solution of 65 g. of sodium bicarbonate in 15 ml. of water. After 10 minutes the phases were separated. The aqueous phase was extracted with dichloromethane. The combined organics were dried with magnesium sulfate, filtered, and concentrated to afford the desired amine.

(c) To residue of the amine prepared in step (b) and 27.4 mg.

(0.201 mmol) of phenylacetic acid in 1.0 ml. of dichloromethane was added 60 μl (0.325 mmol) of diisopropylethylamine followed by 40 μl (0.248 mmol) of diethylcyanophosphonate. After stirring for three hours, the reaction mixture was concentrated and chromatographed on 10 g. of silica gel using 5% to 7% methanol in dichloromethane to afford 80.4 mg. (0.106 mmol, 68%) of the peptide 2R-phenylacetylamino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide. FAM HRMS: $[M + H]^+$ at m/Z = 758.4505 (cal'd for 758.4492).

(d) To a stirred suspension of 42.0 mg. (0.055 mmol) of the peptide prepared in step (c) in dimethylformamide was added 15 mg. of 10% palladium on carbon followed by 38.4 mg. (0.610 mmol) of ammonium formate. The reaction mixture was stirred for five hours at room temperature, then diluted with methanol. The reaction mixture was filtered through celite, catalyst washed with methanol, and the filtrate was concentrated. The residue was chromatographed on silica gel using 5% to 25% methanol in dichloromethane to afford 35.6 mg. (0.053 mmol, 97%) of 2R-phenylacetylamino-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanyl-L-isoleucyl-2-pyridylmethylamide U79,803. FAB HRMS: $[M +H]^+$ at m/Z = 668.4055 (cal'd for 668.4023).

Example 13

(2R-Phenylacetylamino)-glutaryl-5S-amino-4S-hydroxy-2/s-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide (Refer to Chart C)

(a) To a stirred solution of 74.5 mg. (0.221 mmol) of Boc-D-glutamic acid-α-benzyl ester and 86.3 mg. (0.170 mmol) of LVA-Ile-Amp·2HCl in 1.1 ml. of dichloromethane was added 0.13 ml. (0.765 mmol) of diisopropylethyl amine followed by 40 μl (0.272 mmol) of diethylcyanophosphonate. The reaction mixture was stirred at room temperature overnight, concentrated and chromatographed on 15 g. of silica gel using 3% to 5% methanol in dichloromethane to afford 116.6 mg. (0.154 mmol, 91%) of the peptide 2R-tert-Butyloxycarbonyl-amino-1-benzyl-glutaryl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide. FAB HRMS: $[M + H]^+$ at m/Z = 754.4736 (cal'd for 754.4755).

(b) To a stirred solution of 116.6 mg. (0.154 mmol) of the peptide prepared in step (a) in 1.0 ml. of dichloromethane was added 1.0 ml. of trifluoroacetic acid. After 45 minutes at room temperature, the reaction mixture was slowly pipetted into a stirred solution of 1.5

g. of sodium bicarbonate in 15 ml. of water. After 10 minutes the phases were separated. The aqueous phase was extracted with dichloromethane. The combined organics were dried with magnesium sulfate, filtered, and concentrated to afford the desire amine.

(c) To the residue of the amine prepared in step (b) and 27.2 mg. (0.200 mmol) of phenylacetic acid in 1.0 ml. of dichloromethane was added 60 μl (0.323 mmol) of diisopropylethylamine followed by 40 μl (0.246 mmol) of diethylcyanophosphonate. The reaction mixture was stirred at room temperature overnight, concentrated and chromatographed on 13 g. of silica gel using 3% to 5% methanol in dichloromethane to afford 97.7 mg. (0.126 mmol, 82%) of the peptide 2R-phenylacetylamino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethyl amide (21). FAB HRMS: $[M + H]^+$ at m/Z = 772.464 (cal'd for 772.4649).

(d) To a stirred suspension of 37.5 mg. (0.048 mmol) of the peptide in dimethylformamide was added 15 mg. of 10% palladium on carbon followed by 33.7 mg. (0.534 mmol) of ammonium formate. The reaction mixture was stirred for five hours at room temperature, then diluted with methanol. The reaction mixture was filtered through celite, catalyst washed with methanol and the filtrate was concentrated. The residue was chromatographed on silica gel using 20% methanol in dichloromethane to afford (2R-phenylacetylamino)-glutaryl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide. FAB HRMS: $[M + H]^+$ at m/Z = 704.4039 (cal'd for 704.3999).

Example 14

(2S-Phenylacetylamino-succinyl)-5S-amino-4S-hydroxyl-2S-isopropyl-7-methyl-octanoyl-isobutyl amide (Refer to Chart D)

(a) To a stirred solution of 2 g. (4.449 mmol) of the acid, 0.9 ml. (9.0 mmol) of isobutyl amine and 1.0 ml. (5.7 mmol) of diisopropylethyl amine in 20 ml. of dichloromethane was added 0.76 ml. (4.9 mmol) of diethylcyanophosphonate. After stirring at room temperature overnight, the concentrated reaction mixture was chromatographed on silica gel using 15% ethyl acetate in hexane to give compound 5S-t-butyloxycarbonylamino-4S-tert-butyldimethylsilyloxy-2S-isopropyl-7-methyl-octanoyl-isobutyl amide.

(b) To the residue of the amide prepared in step (a) in 3 ml. of dichloromethane was added 3 ml. of trifluoroacetic acid. After 30

minutes at room temperature, the reaction mixture was slowly added to 4 g. of sodium bicarbonate in 40 ml. of water. The aqueous phase was extracted with dichloromethane. Combined organics were dried with magnesium sulfate, filtered and concentrated to give 5S-Amino-4S-tert-butyldimethylsilyloxy-2S-isopropyl-7-methyl-octanoyl-isobutyl amide as a thick paste.

(c) To a stirred solution of 156.8 g. (0.39 mmol) of the amide prepared in step (b) in dichloromethane was added 0.11 ml. (0.63 mmol) of diisopropylethylamine and then 165 mg. (0.51 mmol) of Boc-L-aspartic acid, α-benzyl ester, followed by 80 μl (0.52 mmol) of diethylcyanophosphonate. After a few hours, the concentrated reaction mixture was chromatographed on silica gel using 30% ethyl acetate in hexane to give 150 mg. of the peptide and then eluted with ethyl acetate to give 71.2 mg. of desilylated material.

(d) A solution of 144 mg. of the desilylated material prepared in step (c) in 1 ml. of dichloromethane and 1 ml. of trifluoroacetic acid was stirred at room temperature for 45 minutes. The reaction mixture was slowly added to 2 g. of sodium bicarbonate in 20 ml. of water. The aqueous phase was extracted with dichloromethane. The combined organics were dried with magnesium sulfate, filtered and concentrated to give 100 mg. of the peptide 2S-Amino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-7-isopropyl-methyl-octanoyl-isobutyl amide.

(e) To a stirred solution of 18 mg. (0.13 mmol) of phenylacetic acid, 50.6 mg. (0.1 mmol) of the amide prepared in step (d) and 30 μl (0.17 mmol) of diisopropylethyl amine in 0.5 ml. of dichloromethane was added 20 μl (0.13 mmol) of diethylcyanophosphonate. After a few hours, the concentrated reaction mixture was chromatographed on silica gel using 50% ethyl acetate in dichloromethane to give 57 mg. of the peptide 2S-phenylacetylamino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-isobutyl amide.

(f) A solution of 57 mg. of the peptide prepared in step (e) in 5 ml. of methanol and 50 mg. of 10% palladium on carbon was hydrogenated at 50 psi of hydrogen for four hours. The reaction mixture was filtered through celite with methanol washings. The filtrate was concentrated to give 43.5 mg. of (2S-phenylacetylamino-succinyl)-5S-amino-4S-hydroxyl-2S-isopropyl-7-methyl-octanoyl-isobutyl amide as a white solid. FAB HRMS: $[M + H]^+$ at m/Z = 520.

Example 15

(2S-Phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-isobutylamide (Refer to Chart E)

Steps (a) through (d) are the same as in Example 14.

(e) To a stirred solution of 20 mg. (0.13 mmol) of phenoxyacetic acid, 49 mg. (0.1 mmol) of the amide 2S-amino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-isobutyl amide and 30 μl (0.17 mmol) of diisopropylethyl amine in 0.5 ml. of dichloromethane was added 20 μl (0.13 mmol) of diethylcyanophosphonate. After a few hours, the concentrated reaction mixture was chromatographed on silica gel using 50% ethyl acetate in dichloromethane to give 48 mg. of the peptide 2S-phenoxyacetylamino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-isobutyl amide.

(f) A solution of 48 mg. of peptide in 5 ml. of methanol and 50 mg. of 10% pallaidum on carbon was hydrogenated at 50 psi of hydrogen for four hours. The mixture was filtered through celite with methanol washings. The filtrate was concentrated to give 35.3 mg. of (2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-isobutylamide as a white solid. FAB HRMS: $[M + H]^+$ at m/Z = 536.3351 (cal'd for 536.3336).

Example 16

2S-Thiophenoxyacetylamino-succinyl-5S-amino-4S-hydroxy-isopropyl-7-methyl-octanoyl-isobutyl amide (Refer to Chart E)

Steps (a) thru (d) are the same as in Examples 14 and 15.

(e) To a stirred solution of 55 mg. (0.112 mmol) of 2S-amino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-isobutyl amide 24 mg. (0.14 mmol) of thiophenoxyacetic acetic acid and 30 μl (0.17 mmol) of diisopropylethylamine in 1 ml. of dichloromethane was added 20 μl (0.13 mmol) of diethylcyanophosphonate. After three hours the concentrated reaction mixture was chromatographed on silica gel using 50% ethyl acetate in dichloromethane to afford 54 mg. of peptide 2S-thiophenoxyacetylamino-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-isobutyl-amide.

(f) To a stirred solution of 27 mg. of the peptide prepared in step (e) in 1:1 methanol-tetrahydrofuran was added 0.1 ml. of 1 M aqueous sodium hydroxide. After stirring overnight, the reaction mixture was treated with 0.1 ml. of 1 M aqueous hydrogen chlorine. The solvents were removed via a stream of argon. The residue was partitioned between dichloromethane and 1 M aqueous potassium hydrogen

sulfate. The aqueous phase was extracted with dichloromethane. The combined organic phase was dried with magnesium sulfate and concentrated. The residue was chromatographed on silica gel using 10% to 20% methanol in dichloromethane to give 2S-thiophenoxyacetylamino-succinyl-5S-amino-4S-hydroxy-isopropyl-7-methyl-octanoyl-isobutyl amide as a mixture of epimers. FAB HRMS: $[M + H]^+$ at m/Z = 552.3115 (cal'd for 552.3107).

Example 17

Utilizing procedures similar to those described above but substituting the appropriate derivative amino acids and carboxylic acids for those exemplified above, the following compounds are obtained.

(2S-Phenoxyacetylamino-succinyl)-4S-amino-1-cyano-2SS and 2R, 3R-dihydroxy-5-cyclohexylpentane;

(2S and 2R-Phenoxyacetylamino-succinyl)-4S-amino-1-azido-2S and 2R, 3R-dihydroxy-5-cyclohexylpentane;

(2S-phenoxyacetylamino-succinyl)-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-2S-methylbutylamide;

(2S and 2R-thiophenoxyacetylamino-succinyl)-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethyl-amide;

(2S and 2R-thiophenoxyacetylamino-succinyl)-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-2S-methylbutylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-4-aminobutylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2-(4-imidazolyl)-ethylamide;

2S-(indole-2-carbonylamino)-succinyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-L-isoleucyl-2-pyridylmethylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-4-guanidobutylamide;

2S-(4-pyridylacetylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoly-L-isoleucyl-2-pyridylmethylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2-(4-imidazolyl)-ethylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-5-aminopentylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-3-carboxypropylamide;

(2S-pheoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-4-carboxybutylamide;

2S-(o-methylphenoxyacetylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-isobutylamide;

(2S-phenoxyacetylamino-succinyl)-6S-amino-7-cyclohexyl-4S-5R-dihydroxy-2-methylheptane;

(2S-phenoxyacetylamino-succinyl)-6S-amino-7-cyclohexyl-4R,5R-dihydroxy-2-methylheptane;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2S and 2R-hydroxypropylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-3,2S and 2R-dihydroxypropylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-4-carboxybutylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2S-methylbutylamide;

(2S-phenoxyacetylamino-succinyl)-3S-amino-4-cyclohexyl-2R-hydroxybutanoyl-isopropylester;

(2S-phenoxyacetylamino-succinyl)-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-4-aminobutylamide;

Example 18

(2S-phenoxyacetyloxy-succinyl)-5S-lamino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2S-methylbutylamide (Refer to Chart E)

(a) (Step (a) of Chart E). To a stirred solution of 5S-t-butyloxyycarbonylamino-4S-t-butyldimethylsilyloxy-2S-isopropyl-7-methyloctanoyl-2S-methylbutylamide, prepared as in step (a) of Example 14, in dichloromethane is added trifluoroacetic acid to yield 5S-amino-4S-t-butyldimethylsilyloxy-2S-isopropyl-7-methyloctanoyl-2S-methylbutylamide.

(b) (Step (b) of Chart E). To a stirred solution of 112 mg. (0.50 mmol) of 1-benzyl-S-malate and 173 mg (0.42mmol) of 5S-amino-4S-t-butyldimethylsilyloxy-2S-isopropyl-7-methyloctanoyl-2S-methylbutylamide in 2 ml of dichloromethane was added 87 μl (0.50mmol) of diisopropylethylamine followed by 77 μl (0.50 mmol) of diethylcyanophosphate. The reaction mixture was stirred at room temperature overnight and then concentrated. The reaction mixture was chromatographed on silica gel using 10-20% ethylacetate in dichloromethane and then 5%-10% methanol in dichloromethane to yield 127 mg. of (2S-

hydroxy-1-benzylsuccinyl-5S-amino)-4S-t-butyldimethylsilyloxy-2S-isopropyl-7-methyloctanoyl-2S-methylbutylamide as a yellow solid (49% yield).

(c) (Step (c) of Chart E). To a stirred solution of 65.5 mg (0.11 mmol) of the alcohol prepared in step (b) in 26 mg. (0.21 mmol) of DMAP and 18 μl (0.13 mmol) of phenoxyacetyl chloride is added dropwise. A transient precipitate is formed, but it quickly dissolved giving a yellow solution. This solution was stirred at room temperature and then chromatographed on silica gel using 8%-10% ethyl acetate in dichloromethane to yield 67.6 mg. of 2S-phenoxyacetyloxy-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2S-methylbutylamide as a white solid.

(d) (Step (d) of Chart E). To a stirred solution of 67.6 mg. (89 μmol) of the peptide prepared in step (c) in 1.0 ml. of dichloromethane was added 1.0 ml. of trifluoroacetic acid. After 30 minutes at room temperature, the reaction mixture was slowly pipetted into a stirred solution of 1 g. of sodium bicarbonate in 10 ml. of water. After 10 minutes the phases were separated. The aqueous phase was extracted with dichloromethane. The combined organics were dried with magnesium sulfate, filtered, and concentrated to afford 62 mg. of 2S-phenoxyacetyloxy-1-benzylsuccinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2S-methylbutylamide as a white solid.

(e) (Step (e) of Chart E). To a solution of 89.5 μmol of (2S-phenoxyacetyloxy-1-benzylsuccinyl)-5S-amino-4S-t-hydroxy-2S-isopropyl-7-methyloctanoyl-2S-methylbutylamide in 1 ml. of methanol and 1 ml. of dichloromethanedimethylformamide was shaken under 50 psi of hydrogen in the presence of palladium and carbon for about two hours. The material was chromatographed on silical gel with 10%-20% methanol in dichloromethane to yield 34.2 mg of (2S-phenoxyacetyloxy-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2S-methylbutylamide as a white solid.

Utilizing procedures similar to those described in Example 18 above but substituting the appropriate derivative amino acids and acyl chlorides for those exemplified in that example, the following compounds are obtained:

(2S-phenoxyacetyloxy-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2S-methylbutylamide;

(2S-phenylacetyloxy-succinyl)-5S-amino-4S-hydroxy-2S-iso-

propyl-7-methyloctanoyl-2S-methylbutylamide;

(2S-phenylacetyloxy-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-L-isoleucyl-2-pyridylmethylamide;

(2S-phenoxyacetyloxy-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-L-isoleucyl-2-pyridylmethylamide;

(2S-phenoxyacetyloxy-succinyl)-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-4-carboxybutylamide;

(2S-phenoxyacetyloxy-succinyl)-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-2S-methylbutamide;

(2S-phenoxyacetyloxy-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2R and 2S-hydroxypropylamide;

(2S-phenoxyacetyloxy-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2R and2S,3-dihyroxypropylamide;

(2S-phenoxyacetyloxy-succinyl)-3S-amino-4-cyclohexyl-2R-hydroxybutanoyl-isopropylester;

(2S-phenoxyacetyloxy-succinyl)-6S-amino-7-cyclohexyl-4S,5R-dihydroxy-2-methylheptane;

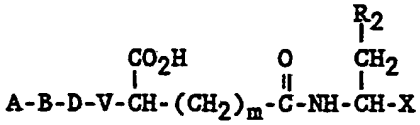
(2S-phenoxyacetyloxy-succinyl)-6S-amino-7-cyclohexyl-4R,5R-dihydroxy-2-methylheptane;

(2S-phenoxyacetyloxy-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-4-aminobutylamide;

(2S-phenoxyacetyloxy-succinyl)-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-4-aminobutylamide.

FORMULAS

I



IC

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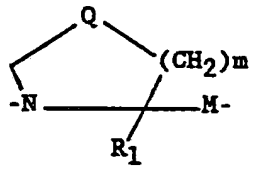

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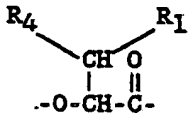

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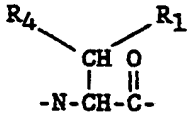
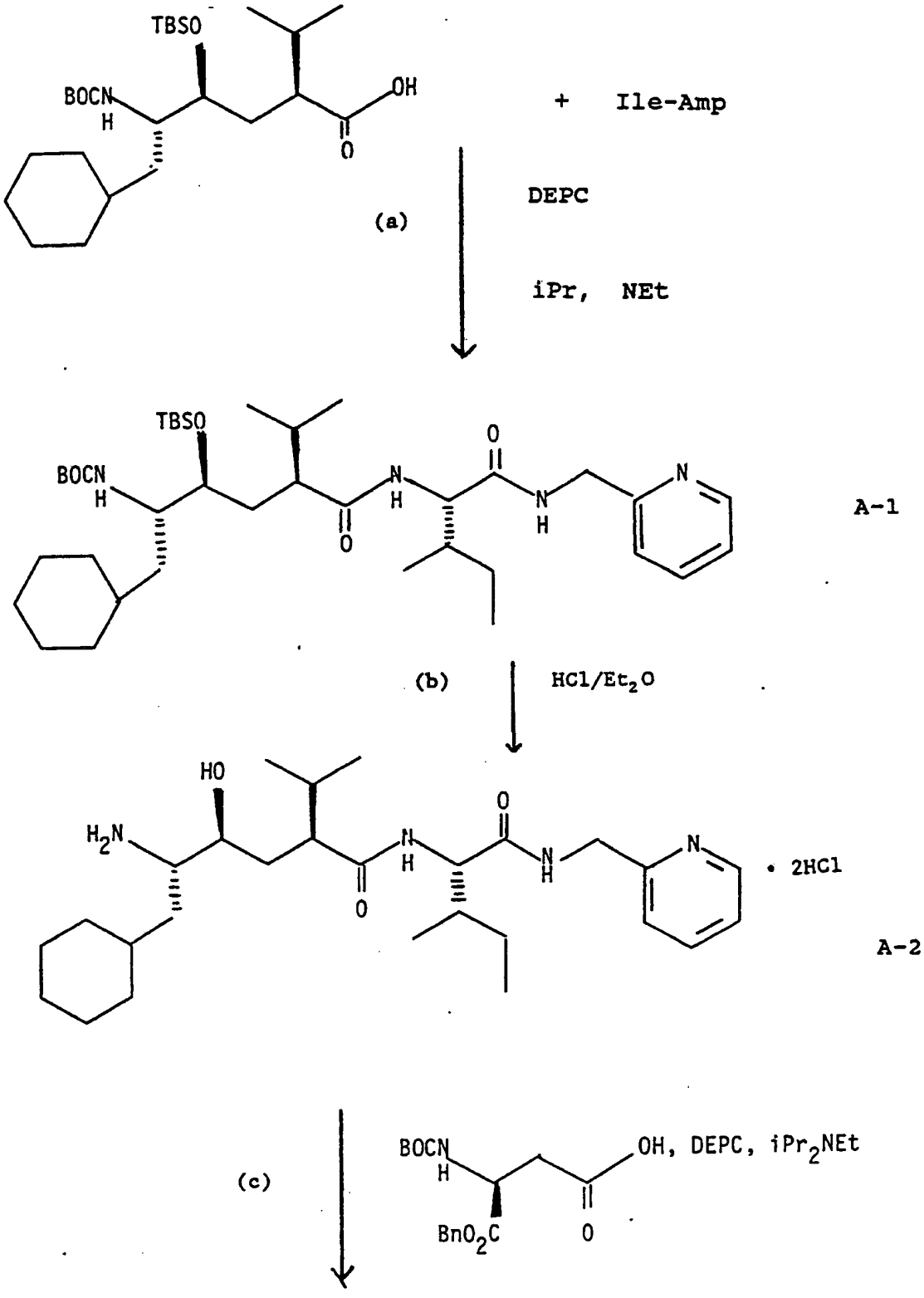


L3

CHART A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OH
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DEPC
iPr, NEt
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N
H
O
N
H
N
A-1
(b)
HCl/Et2O
HO
H2N
O
N
H
O
N
H
N
• 2HCl
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(c)
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OH, DEPC, iPr2NEt
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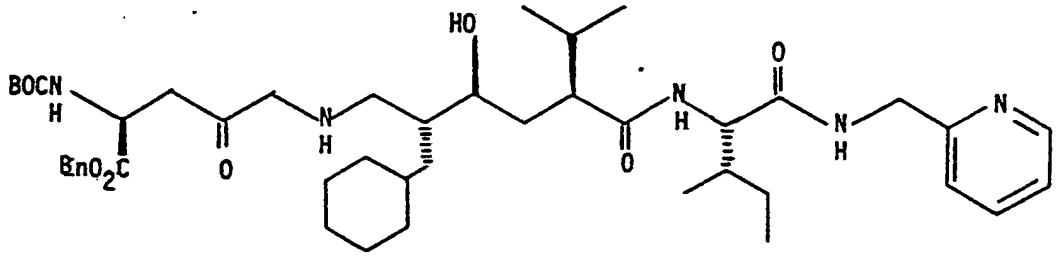
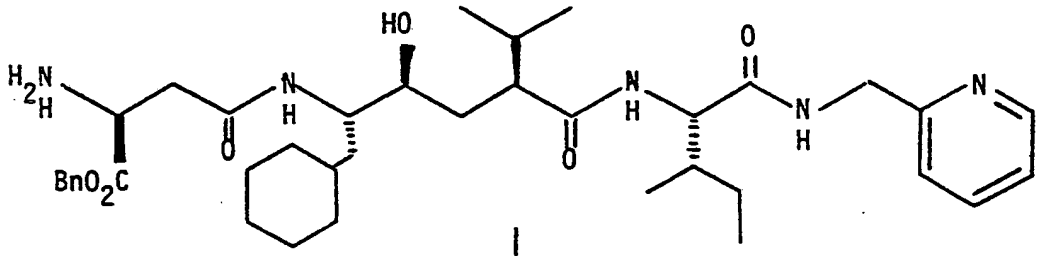
O

CHART A (CONTINUED)



A-3

(d) TFA/CH_2Cl_2

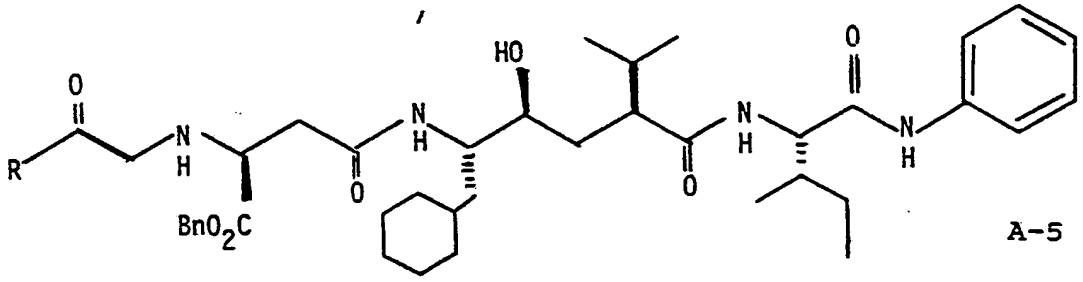


A-4

(e) RCOOH

R = phenyl

R = phenoxy

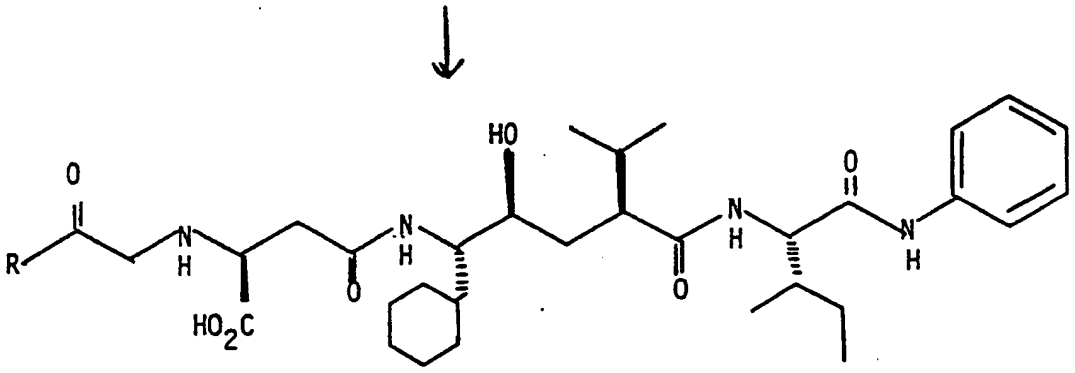


A-5

R = phenyl, phenoxy
thiophenoxy

(f) $HCOONH_4$
DMF
Pd-C

CHART A (CONTINUED)

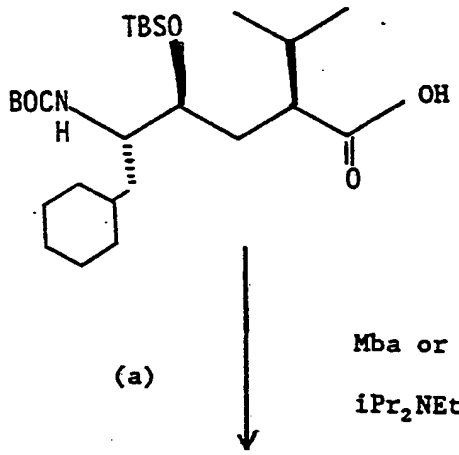


A-6

R = phenyl A-6a

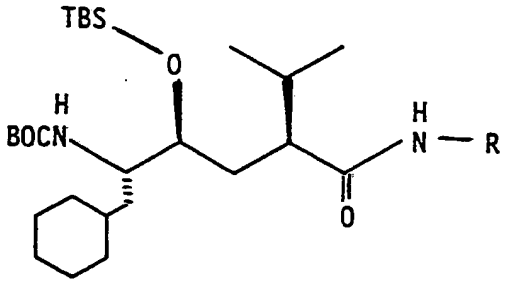
R = phenoxy A-6b

CHART B



(a) Mba or CH_3NH_2

iPr_2NEt, DEPC



9a (R = Mba)

9b (R = CH_3)

B-1

(b) a) HCR_1, Et_2O

(c)

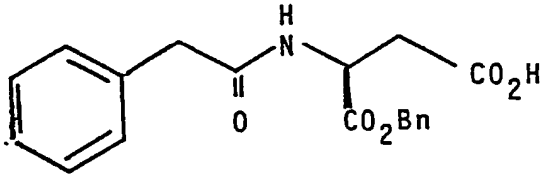
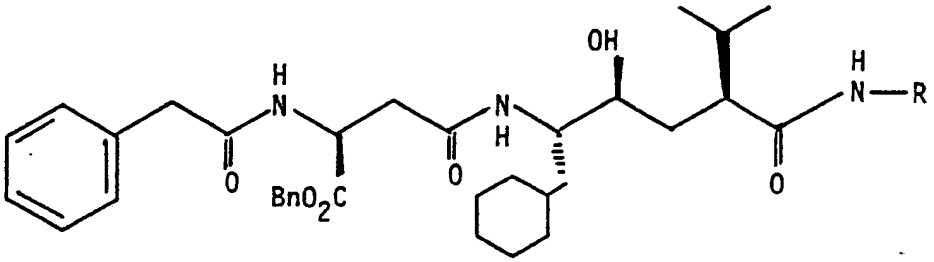
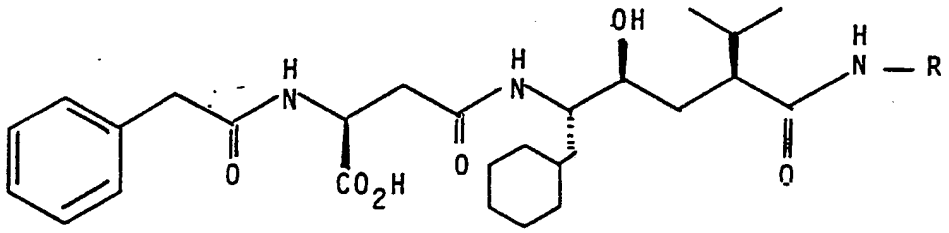


CHART B (CONTINUED



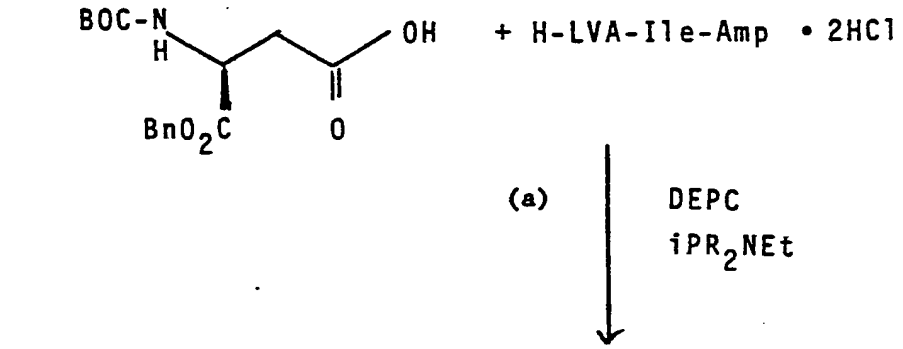
R = CH_3, Mba

(d) H_2, Pd/C



R = CH_3, Mba

CHART C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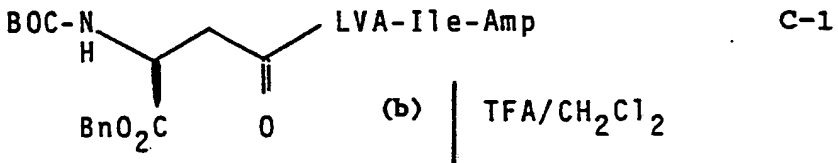
BnO2C
O
(a)
DEPC
iPR2NEt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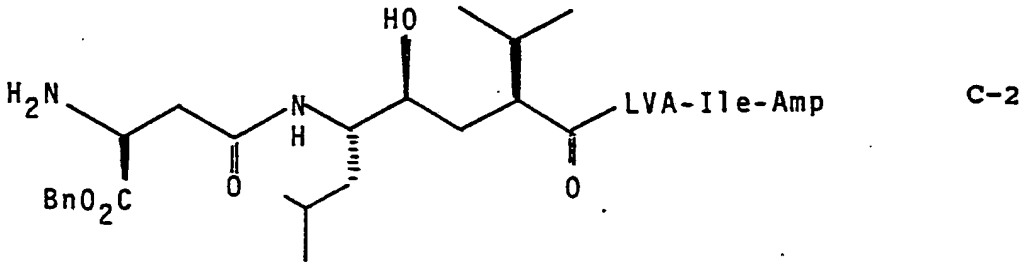
LVA-Ile-Amp
C-1
BnO2C
O
(b)
TFA/CH2Cl2


HO
H2N
N
H
LVA-Ile-Amp
C-2
BnO2C
O
O

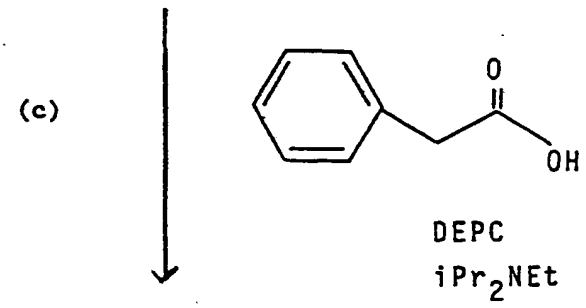
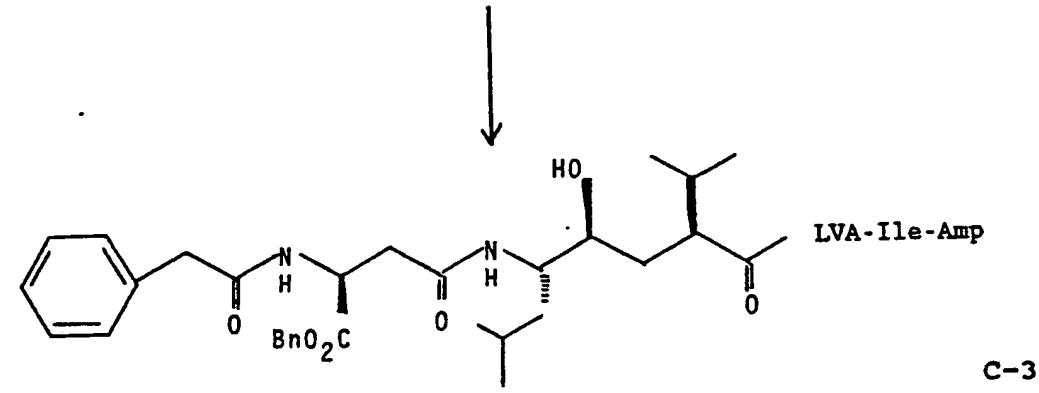
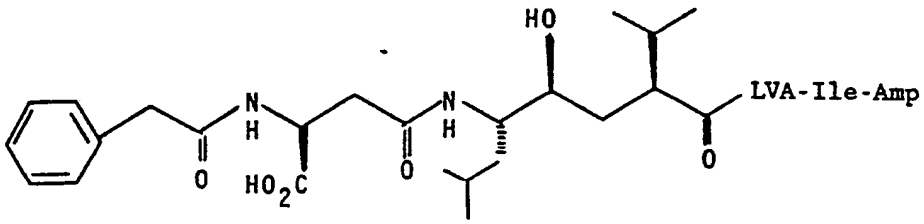

(c)
O
OH
DEPC
iPr2NEt

CHART C (CONTINUED)



C-3

(d) $HCOONH_4$, DMF, Pd-C



C-4

CHART D

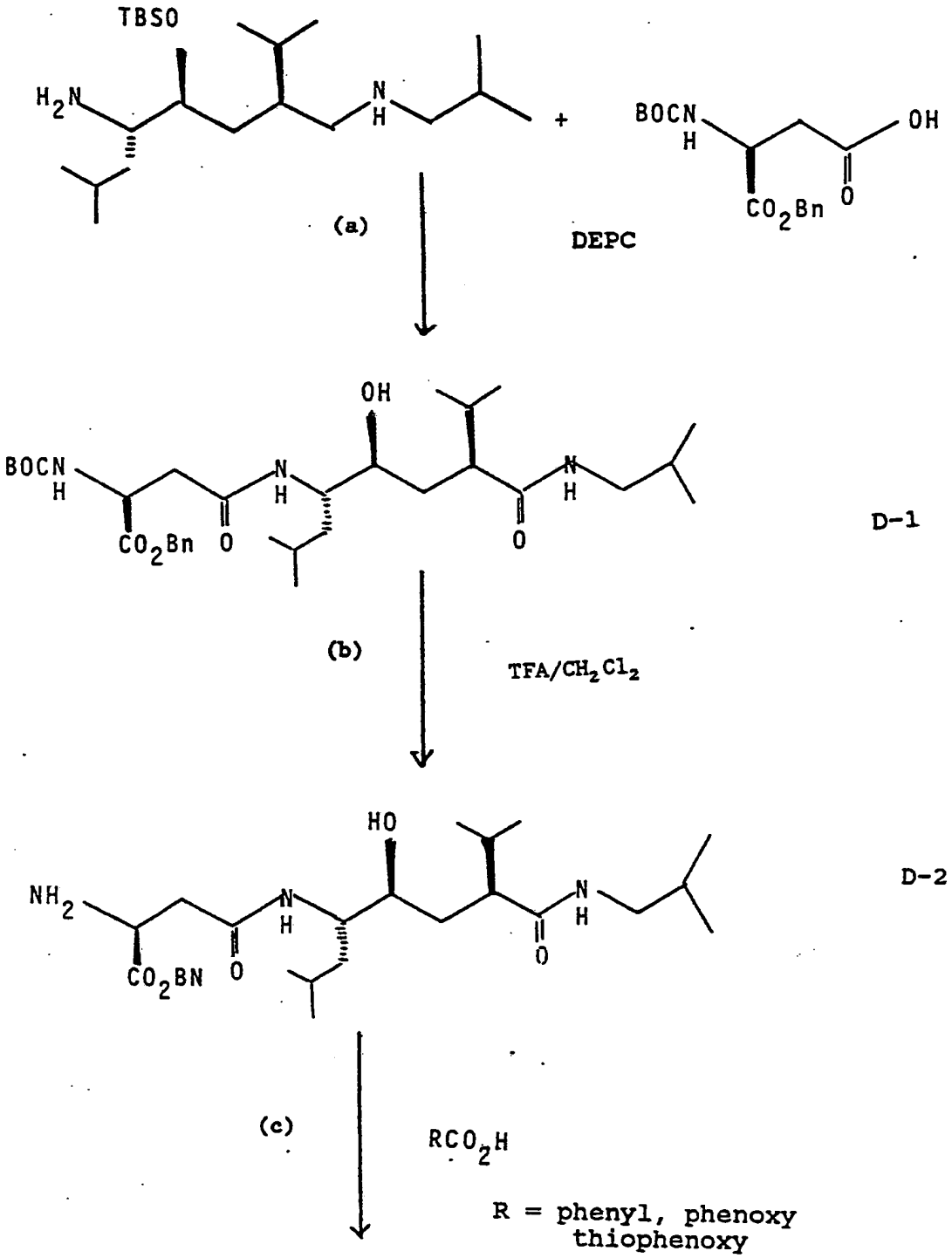
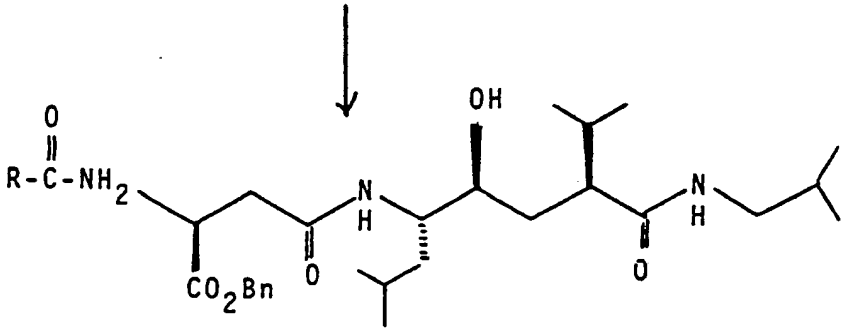
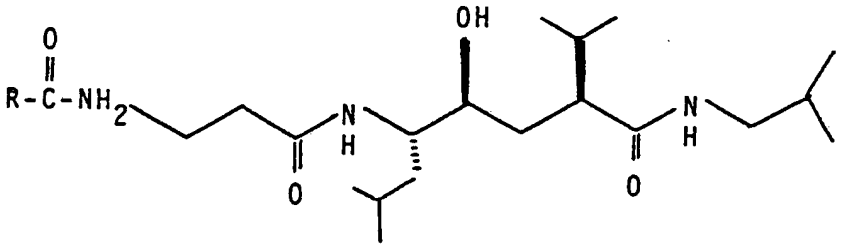

TBSO
H2N
N
H
+
BOCN
H
OH
O
CO2Bn
(a)
DEPC
OH
BOCN
H
N
H
N
H
CO2Bn
O
O
D-1
(b)
TFA/CH2Cl2
HO
NH2
N
H
N
H
CO2BN
O
O
D-2
(c)
RCO2H
R = phenyl, phenoxy
thiophenoxy

CHART D (CONTINUED)



D-3

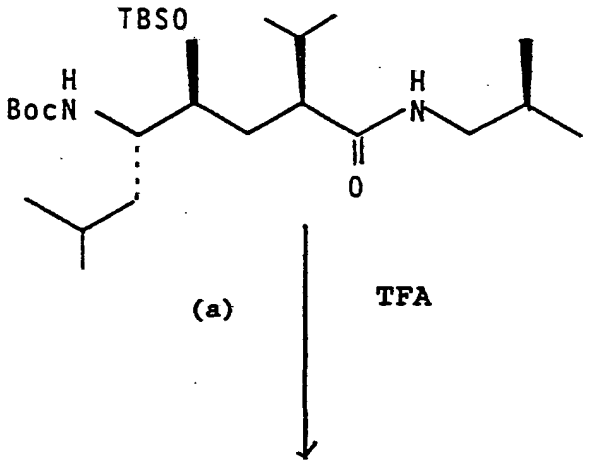
(d) H_2/PD-C



D-4

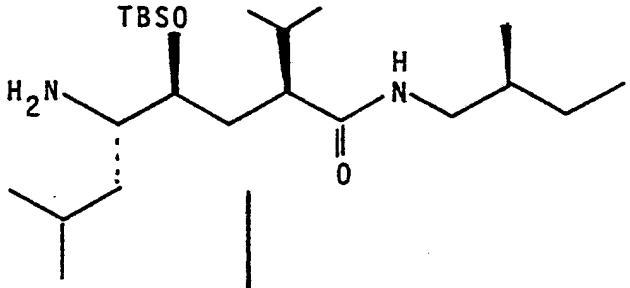
R = phenyl, phenoxy
thiophenoxy

CHART E



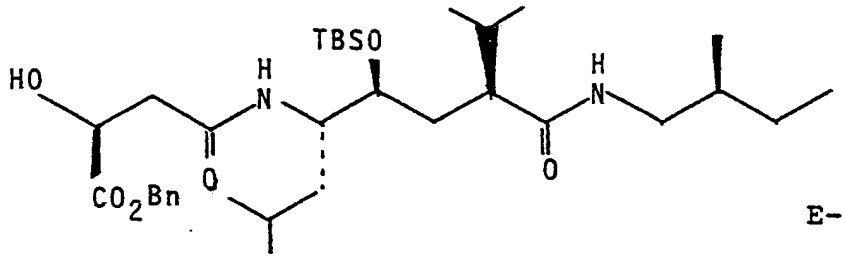
E-1

(a) TFA



E-2

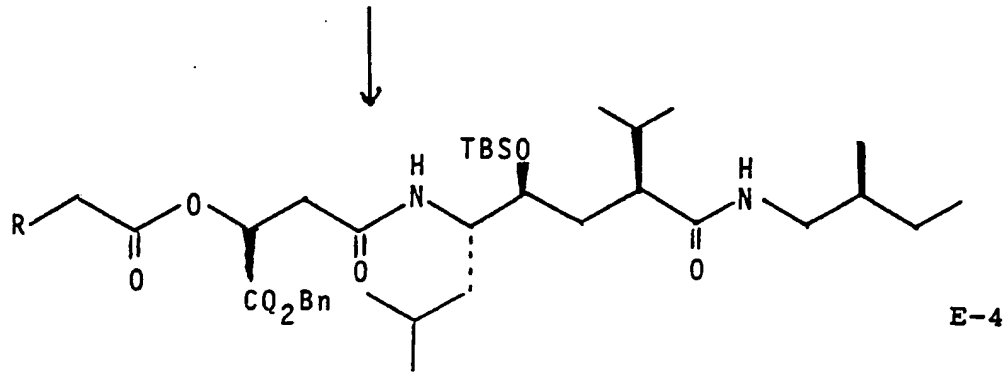
(b) Benzyl-S-malate



E-3

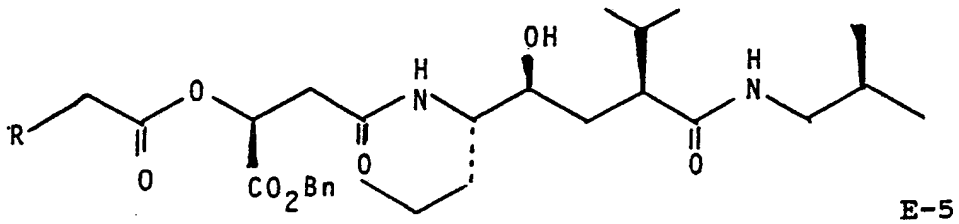
(c) RCOCl
DMAP

CHART E (CONTINUED)



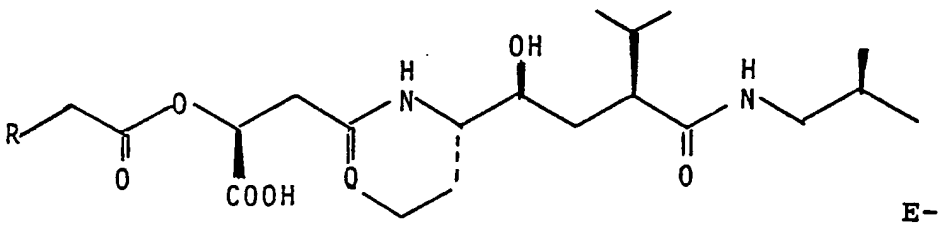
E-4

(d) TFA



E-5

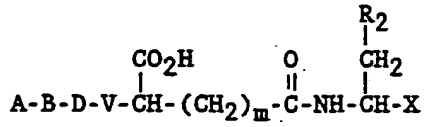
(e) H_2, Pd/C



E-6

CLAIMS

1. The renin inhibitory peptide of the Formula I



wherein A is

(a) hydrogen,

(b) C_1-C_5 alkyl,

(c) R_3-O-$(CH_2)_q$-C(O)-,

(d) R_3-$(CH_2)_q$-O-C(O),

(e) R_3-O-C(O),

(f) R_3-$(CH_2)_n$-C(O),

(g) $R_1N(R_1)$-$(CH_2)_n$-C(O),

(h) R_3SO_2-$(CH_2)_n$-C(O),

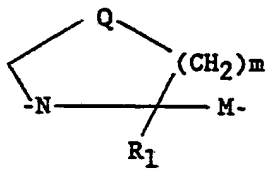
(i) R_3SO_2-$(CH_2)_n$-O-C(O),

(j) R_3S-$(CH_2)_q$-C(O)-,

(k) R_3-$(CH_2)_q$-S-$(CH_2)_n$-C(O)-, or

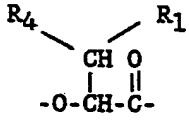
(l) R_3-$(CH_2)_q$-O-$(CH_2)_n$-C(O)-;

wherein B is absent or a divalent moiety of the formula L_1:

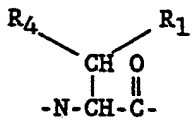


L_1

wherein D is absent or a divalent moiety of the formula L_2 or L_3:



L_2



L_3

wherein V is oxygen or -N(R_1)-;

wherein X is

-CH(OH)-CH(OH)-CH_2-P,

-E-C(R_1)(R_4)-C(O)-F-Z or

-J-C(K_1)(K_2)-C(O)-F-Z

wherein P is

(a) $-N_3$,

(b) -CN,

(c) C_1-C_6 alkyl,

(d) C_1-C_6 cycloalkyl,

(e) aryl, or

(f) Het;

wherein E is a divalent moiety of the formula:

(a) -CH(OH)-,

(b) -CH(NH_2);

(c) -C(O)-,

(d) -CH(OH)-CH(OH)-,

(e) -CH(OH)-CH_2-,

(f) -CH(NH_2)-CH_2-,

(g) -C(O)-CH_2-,

(h) -CH_2-NH-,

(i) -CH_2-O-, or

(j) -P(O)(G)-H-;

wherein F is absent or a divalent moiety of the formula L_3;

wherein G is -OH or NH_2;

wherein H is -O-, -NH-, or -CH_2-;

wherein J is -CH(OH)-, -CH(NH_2)-, or -C(O)-;

where Q is

(a) -CH_2-,

(b) -CH(OH)-,

(c) -O-, or

(d) -S-;

wherein M is

(a) -C(O)-, or

(b) -CH_2-;

wherein K_1 and K2 are H, F, or Cl;

wherein Z is -O-R_5 or -N(R_1)R_5;

wherein R_1 is

(a) hydrogen, or

(b) C_1-C_5 alkyl;

wherein R_2 is

(a) hydrogen

(b) C_1-C_5 alkyl;
(c) C_3-C_7 cyclcoalkyl,
(d) aryl,
(e) het,
(f) $-(CH_2)_p-OH$, or
(g) $-(CH_2)_p-NH_2$;

wherein R_3 is
(a) C_1-C_5 alkyl,
(b) C_3-C_7 cycloalkyl,
(c) aryl, or
(d) het;

wherein R_4 is
(a) hydrogen,
(b) C_1-C_5 alkyl,
(c) $-(CH_2)_p$-aryl,
(d) $-(CH_2)_p$-het,
(e) C_3-C_7 cycloalkyl, or
(f) 1- or 2-adamantyl;

wherein R_5 is
(a) hydrogen,
(b) aryl,
(c) het,
(d) C_1-C_{10} alkyl,
(e) $-(CH_2)_p-(C_3$-C_7 cycloalkyl), or
(f) $-(CH_2)_n-R_6$;

wherein R_6 is
(a) aryl,
(b) het,
(c) hydroxy,
(d) amino,
(e) polyhydroxylated alkyl,
(f) -COOH,
(g) guanidyl, or
(h) $-SO_3H$;

wherein m is 1 or 2;
wherein n is 1 to 5, inclusive;
wherein p is 0 to 5, inclusive;
wherein q is 1 to 5, inclusive;

wherein Aryl is phenyl or naphthyl substituted by zero to 3 of the following:

(a) C_1-C_3 alkyl,
(b) hydroxy,
(c) hydroxy(C_1-C_3 alkyl),
(d) halogen,
(e) amino,
(f) amino(C_1-C_3 alkyl),
(g) -CHO,
(h) $-CO_2H$,
(i) $-CO_2$-(C_1-C_3 alkyl),
(j) $-CONH_2$,
(k) -CONH-(C_1-C_3 alkyl),
(l) nitro,
(m) mercapto,
(n) mercapto(C_1-C_3 alkyl),
(o) $-SO_3H$,
(p) $-SO_2NH_2$,
(q) -CN-;

wherein HET is a 5 ot 6-membered saturated or unsaturated ring containing from one to three heteroatoms (nitrogen, oxygen, sulfur); and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; and, if chemically feasible, the nitrogen and sulfur atoms may be in the oxidized forms;

or a carboxy-, amino- or other reactive group-protected form thereof;

or a pharmaceutically acceptable acid or base addition salts thereof.

2. A compound according to claim 1 having the formula IC

A-V-C(H)(COOH)-(CH2)m-C(O)-N(H)-C(H)(CH2R2)-CH(OH)CH2-C(R4)(R1)C(O)-F-Z

wherein A is selected from the group consisting of R_3-O-$(CH_2)_q$-C(O)-, R_3-$(CH_2)_n$-C(O)- and R_3S-$(CH_2)_q$-C(O)-; V is oxygen or -N(R1)-; R_2 is C_1-C_5 alkyl or C_3-C_7 cycloalkyl; R_1 is hydrogen or C_1-C_5 alkyl; R_4 is

hydrogen or C_1-C_5 alkyl; F is absent or a divalent moiety of the formula L_3; and Z is $N(R_1)R_5$ wherein R_5 is (C_1-C_{10}) alkyl or -(CH_2)-Het.

3. A compound of claim 2 wherein the moieties at the 2, 4 and 5 carbon atoms of the transition-state insert are in the S configuration.

4. A compound according to claim 2 wherein V is -N(R1)- and m is selected from the group consisting of

2R-phenylacetylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide;

(2S-phenoxyacetylamino-succinyl)-4S-amino-1-cyano-2S and 2R, 3R-dihydroxy-5-cyclohexylpentane;

(2S and 2R-thiophenoxyacetylamino-succinyl)-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-L-isoleucyl-2-pyridylmethylamide;

(2S and 2R-thiophenoxyacetylamino-succinyl)-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropyl-hexanoyl-2S-methylbutylamide;

(2S-phenoxyacetylamino-succinyl)-6S-amino-7-cyclohexyl-4S-5R-dihydroxy-2-methylheptane;

(2S-phenoxyacetylamino-succinyl)-6S-amino-7-cyclohexyl-4R,5R-dihydroxy-2-methylheptane;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2S and 2R-hydroxypropylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-3,2S and 2R-dihydroxypropylamide;

(2S-phenoxyacetylamino-succinyl)-3S-amino-4-cyclohexyl-2R-hydroxybutanoyl-isopropylester.

5. A compound of claim 3 wherein V is -N(R_1)- and m is 1 selected from the group consisting of

2S-phenylacetylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-6-cyclohexylmethylhexanoyl-L-isoleucyl-2-pyridylmethylamide;

(2S-phenoxyacetylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide;

2S-phenylacetylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide;

2S-phenylacetylamino)-succinyl-5S-amino-4S-hydroxy-2S-

isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide arginine salt;

(2S-benzoylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide;

[2S-(3-pyridinyl)acetylamino]-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridymethylamide;

2S-phenylacetylamino-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-6-cyclohexylmethylhexanoyl-L-isoleucyl-2-pyridylmethylamide;

2S-thiophenoxyacetylamino-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-isobutylamide;

phenylacetyl-β-L-aspartyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoylmethylamide;

phenylacetyl-β-L-aspartyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-2S-methylbutylamide;

[2S-(2-pyridinyl)acetylamino]-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide;

(2S-phenoxyacetylamino-succinyl)5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-isobutylamide;

(2S-phenylacetylamino-succinyl)-5S-amino-4S-hydroxyl-2S-isopropyl-7-methyl-octanoyl-isobutylamide;

(2S and 2R-phenoxyacetylamino-succinyl)-4S-amino-1-azido-2S and 2R, 3R-dihydroxy-5-cyclohexylpentane;

(2S-phenoxyacetylamino-succinyl)-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-2S-methylbutylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-4-aminobutylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2-(4-imidazolyl)-ethylamide;

2S-(indole-2-carbonylamino)-succinyl-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-L-isoleucyl-2-pyridylmethylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-4-guanidobutylamide;

2S-(4-pyridylacetylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoly-L-isoleucyl-2-pyridylmethylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2-(4-imidazolyl)-ethylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-5-aminopentylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-3-carboxypropylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-4-carboxybutylamide;

2S-(o-methylphenoxyacetylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-isobutylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-4-carboxybutylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2S-methylbutylamide;

(2S-phenoxyacetylamino-succinyl)-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-4-aminobutylamide.

6. A compound of claim 5, 2S-phenylacetylamino)-succinyl-5S-amino-4S-hydroxy-2S-isopropyl-6-cyclohexylmethylhexanoyl-L-isoleucyl-2-pyridyl-methylamide.

7. A compound according to claim 2 wherein V is -N(R_1- and m is 2, (2R-phenylacetylamino)-glutaryl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide.

8. A compound according to claim 3 wherein V is -N(R_1)- and m is 2 selected from the group consisting of

(2S-phenoxyacetylamino)-glutaryl-5S-amino-4S-hydroxy-S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide;

(2S-phenylacetylamino)-glutaryl-5S-amino-4S-hydroxy-2S-isopropyl-7-methyl-octanoyl-L-isoleucyl-2-pyridylmethylamide;

9. A compound according to claim 2 wherein V is oxygen and m is 1 selected from the group consisting of

(2S-phenoxyacetyloxy-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2R and 2S-hydroxypropylamide;

(2S-phenoxyacetyloxy-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2R and2S,3-dihyroxypropylamide;

(2S-phenoxyacetyloxy-succinyl)-3S-amino-4-cyclohexyl-2R-hydroxybutanoyl-isopropylester;

(2S-phenoxyacetyloxy-succinyl)-6S-amino-7-cyclohexyl-4S,5R-dihydroxy-2-methylheptane;

(2S-phenoxyacetyloxy-succinyl)-6S-amino-7-cyclohexyl-4R,5R-dihydroxy-2-methylheptane.

10. A compound according to claim 3, wherein V is oxygen and m is 1 selected from the group consisting of

(2S-phenoxyacetyloxy-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2S-methylbutylamide;

(2S-phenylacetyloxy-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-2S-methylbutylamide;

(2S-phenylacetyloxy-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-L-isoleucyl-2-pyridylmethylamide;

(2S-phenoxyacetyloxy-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-L-isoleucyl-2-pyridylmethylamide;

(2S-phenoxyacetyloxy-succinyl)-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-4-carboxybutylamide;

(2S-phenoxyacetyloxy-succinyl)-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-2S-methylbutamide;

(2S-phenoxyacetyloxy-succinyl)-5S-amino-4S-hydroxy-2S-isopropyl-7-methyloctanoyl-4-aminobutylamide;

(2S-phenoxyacetyloxy-succinyl)-5S-amino-6-cyclohexyl-4S-hydroxy-2S-isopropylhexanoyl-4-aminobutylamide.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 88/03436

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC4: C 07 K 5/02, C 07 C 103/49

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC4	C 07 K; C 07 C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	DE, A1, 36 01 248 (HOECHST AG) 23 July 1987, see the whole document --	1-10
A	DE, A1, 36 10 593 (HOECHST AG) 1 October 1987, see the whole document --	1-10
A	EP, A2, 0 209 848 (MERCK & CO.INC.) 28 January 1987, see the whole document --	1-10
A	EP, A2, 0 244 836 (DAINIPPON PHARMACEUTICAL CO., LTD.) 11 November 1987, see the whole document --	1-10

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
9th February 1989	- 7. 03. 89
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/US 88/03436

SA 25659

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 12/01/89
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